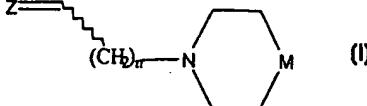


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(54) Title: CHEMOKINE RECEPTOR ANTAGONISTS AND METHODS OF USE THEREFOR			
			
(57) Abstract			
<p>Disclosed are novel compounds and a method of treating a disease associated with aberrant leukocyte recruitment and/or activation. The method comprises administering to a subject in need an effective amount of a compound represented by structural formula (I) and physiologically acceptable salts thereof.</p>			

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CHEMOKINE RECEPTOR ANTAGONISTS
AND METHODS OF USE THEREFOR

RELATED APPLICATIONS

- This application is a continuation-in-part of U.S.
- 5 Serial No. 09/148,823, filed September 4, 1998, which is a continuation-in-part of U.S. Serial No. 09/010,320, filed January 21, 1998, now abandoned, the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

- 10 Chemoattractant cytokines or chemokines are a family of proinflammatory mediators that promote recruitment and activation of multiple lineages of leukocytes and lymphocytes. They can be released by many kinds of tissue

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cells after activation. Continuous release of chemokines at sites of inflammation mediates the ongoing migration of effector cells in chronic inflammation. The chemokines characterized to date are related in primary structure.

- 5 They share four conserved cysteines, which form disulfide bonds. Based upon this conserved cysteine motif, the family is divided into two main branches, designated as the C-X-C chemokines (α -chemokines), and the C-C chemokines (β -chemokines), in which the first two conserved cysteines
10 are separated by an intervening residue, or adjacent respectively (Baggiolini, M. and Dahinden, C. A.,
Immunology Today, 15:127-133 (1994)).

The C-X-C chemokines include a number of potent chemoattractants and activators of neutrophils, such as
15 interleukin 8 (IL-8), PF4 and neutrophil-activating peptide-2 (NAP-2). The C-C chemokines include RANTES (Regulated on Activation, Normal T Expressed and Secreted), the macrophage inflammatory proteins 1 α and 1 β (MIP-1 α and MIP-1 β), eotaxin and human monocyte chemotactic
20 proteins 1-3 (MCP-1, MCP-2, MCP-3), which have been characterized as chemoattractants and activators of monocytes or lymphocytes but do not appear to be chemoattractants for neutrophils. Chemokines, such as RANTES and MIP-1 α , have been implicated in a wide range of
25 human acute and chronic inflammatory diseases including respiratory diseases, such as asthma and allergic disorders.

The chemokine receptors are members of a superfamily of G protein-coupled receptors (GPCR) which share

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structural features that reflect a common mechanism of action of signal transduction (Gerard, C. and Gerard, N.P., *Annu Rev. Immunol.*, 12:775-808 (1994); Gerard, C. and Gerard, N. P., *Curr. Opin. Immunol.*, 6:140-145 (1994)).

- 5 Conserved features include seven hydrophobic domains spanning the plasma membrane, which are connected by hydrophilic extracellular and intracellular loops. The majority of the primary sequence homology occurs in the hydrophobic transmembrane regions with the hydrophilic
10 regions being more diverse. The first receptor for the C-C chemokines that was cloned and expressed binds the chemokines MIP-1 α and RANTES. Accordingly, this MIP-1 α /RANTES receptor was designated C-C chemokine receptor 1 (also referred to as CCR-1; Neote, K., et al.,
15 *Cell*, 72:415-425 (1993); Horuk, R. et al., WO 94/11504, May 26, 1994; Gao, J.-I. et al., *J. Exp. Med.*, 177:1421-1427 (1993)). Three receptors have been characterized which bind and/or signal in response to RANTES: CCR3 mediates binding and signaling of chemokines including eotaxin,
20 RANTES, and MCP-3 (Ponath et al., *J. Exp. Med.*, 183:2437 (1996)), CCR4 binds chemokines including RANTES, MIP-1 α , and MCP-1 (Power, et al., *J. Biol. Chem.*, 270:19495 (1995)), and CCR5 binds chemokines including MIP-1 α , RANTES, and MIP-1 β (Samson, et al., *Biochem.* 35: 3362-3367
25 (1996)). RANTES is a chemotactic chemokine for a variety of cell types, including monocytes, eosinophils, and a subset of T-cells. The responses of these different cells may not all be mediated by the same receptor, and it is possible that the receptors CCR1, CCR4 and CCR5 will show

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some selectivity in receptor distribution and function between leukocyte types, as has already been shown for CCR3 (Ponath et al.). In particular, the ability of RANTES to induce the directed migration of monocytes and a memory 5 population of circulating T-cells (Schall, T. et al., *Nature*, 347:669-71 (1990)) suggests this chemokine and its receptor(s) may play a critical role in chronic inflammatory diseases, since these diseases are characterized by destructive infiltrates of T cells and 10 monocytes.

Many existing drugs have been developed as antagonists of the receptors for biogenic amines, for example, as antagonists of the dopamine and histamine receptors. No successful antagonists have yet been developed to the 15 receptors for the larger proteins such as chemokines and C5a. Small molecule antagonists of the interaction between C-C chemokine receptors and their ligands, including RANTES and MIP-1 α , would provide compounds useful for inhibiting harmful inflammatory processes "triggered" by receptor 20 ligand interaction, as well as valuable tools for the investigation of receptor-ligand interactions.

SUMMARY OF THE INVENTION

It has now been found that a class of small organic 25 molecules are antagonists of chemokine receptor function and can inhibit leukocyte activation and/or recruitment. An antagonist of chemokine receptor function is a molecule which can inhibit the binding and/or activation of one or more chemokines, including C-C chemokines such as RANTES,

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MIP-1 α , MCP-2, MCP-3 and MCP-4 to one or more chemokine receptors on leukocytes and/or other cell types. As a consequence, processes and cellular responses mediated by chemokine receptors can be inhibited with these small organic molecules. Based on this discovery, a method of treating a disease associated with aberrant leukocyte recruitment and/or activation is disclosed as well as a method of treating a disease mediated by chemokine receptor function. The method comprises administering to a subject in need an effective amount of a compound or small organic molecule which is an antagonist of chemokine receptor function. Compounds or small organic molecules which have been identified as antagonists of chemokine receptor function are discussed in detail hereinbelow, and can be used for the manufacture of a medicament for treating or for preventing a disease associated with aberrant leukocyte recruitment and/or activation. The invention also relates to the disclosed compounds and small organic molecules for use in treating or preventing a disease associated with aberrant leukocyte recruitment and/or activation. The invention also includes pharmaceutical compositions comprising one or more of the compounds or small organic molecules which have been identified herein as antagonists of chemokine function and a suitable pharmaceutical carrier. The invention further relates to novel compounds which can be used to treat an individual with a disease associated with aberrant leukocyte recruitment and/or activation and methods for their preparation.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic showing the preparation of the compounds represented by Structural Formula (I).

Figure 2 is a schematic showing the preparation of the 5 compounds represented by Compound (VI-b).

Figure 3 is a schematic showing the preparation of the compounds represented by Structural Formula (I)

Figure 4 is a schematic showing the preparation of the compounds represented by Structural Formula (I), wherein Z 10 is represented by Structural Formula (III) and wherein Ring A and/or Ring B in Z is substituted with R⁴⁰.

Figure 5 is a schematic showing the preparation of the compounds represented by Structural Formula (I), wherein Z 15 is represented by Structural Formula (III) and wherein Ring A and/or Ring B in Z is substituted with

- (O)_u-(CH₂)_t-COOR²⁰, - (O)_u-(CH₂)_t-OC(O)R²⁰,
- (O)_u-(CH₂)_t-C(O)-NR²¹R²² or - (O)_u-(CH₂)_t-NHC(O)O-R²⁰.

Figures 6A-6Z show the structures of exemplary compounds of the present invention.

20 Figure 7 shows the preparation of compounds represented by Structural Formula (I), where in Z is represented by Structural Formulas (III) and wherein Ring A or Ring B in Z is substituted with R⁴⁰.

DETAILED DESCRIPTION OF THE INVENTION

25 The present invention relates to small molecule compounds which are modulators of chemokine receptor function. In a preferred embodiment, the small molecule compounds are antagonists of chemokine receptor function.

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Accordingly, processes or cellular responses mediated by the binding of a chemokine to a receptor can be inhibited (reduced or prevented, in whole or in part), including leukocyte migration, integrin activation, transient 5 increases in the concentration of intracellular free calcium $[Ca^{++}]_i$, and/or granule release of proinflammatory mediators.

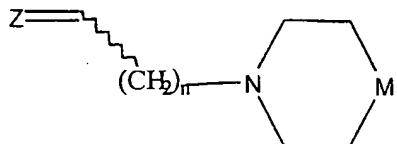
The invention further relates to a method of treatment, including prophylactic and therapeutic 10 treatments, of a disease associated with aberrant leukocyte recruitment and/or activation or mediated by chemokines or chemokine receptor function, including chronic inflammatory disorders characterized by the presence of RANTES, MIP-1 α , MCP-2, MCP-3 and/or MCP-4 responsive T cells, monocytes 15 and/or eosinophils, including but not limited to diseases such as arthritis (e.g., rheumatoid arthritis), atherosclerosis, arteriosclerosis, ischemia/reperfusion injury, diabetes mellitus (e.g., type 1 diabetes mellitus), psoriasis, multiple sclerosis, inflammatory bowel diseases 20 such as ulcerative colitis and Crohn's disease, rejection of transplanted organs and tissues (i.e., acute allograft rejection, chronic allograft rejection), graft versus host disease, as well as allergies and asthma. Other diseases associated with aberrant leukocyte recruitment and/or 25 activation which can be treated (including prophylactic treatments) with the methods disclosed herein are inflammatory diseases associated with Human Immunodeficiency Virus (HIV) infection, e.g., AIDS associated encephalitis, AIDS related maculopapular skin

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- eruption, AIDS related interstitial pneumonia, AIDS related enteropathy, AIDS related periportal hepatic inflammation and AIDS related glomerulo nephritis. The method comprises administering to the subject in need of treatment an effective amount of a compound (i.e., one or more compounds) which inhibits chemokine receptor function, inhibits the binding of a chemokine to leukocytes and/or other cell types, and/or which inhibits leukocyte migration to, and/or activation at, sites of inflammation.
- The invention further relates to methods of antagonizing a chemokine receptor, such as CCR1, in a mammal comprising administering to the mammal a compound as described herein.
- According to the method, chemokine-mediated chemotaxis and/or activation of pro-inflammatory cells bearing receptors for chemokines can be inhibited. As used herein, "pro-inflammatory cells" includes but is not limited to leukocytes, since chemokine receptors can be expressed on other cell types, such as neurons and epithelial cells.
- While not wishing to be bound by any particular theory or mechanism, it is believed that compounds of the invention are antagonists of the chemokine receptor CCR1, and that therapeutic benefits derived from the method of the invention are the result of antagonism of CCR1 function. Thus, the method and compounds of the invention can be used to treat a medical condition involving cells which express CCR1 on their surface and which respond to signals transduced through CCR1, as well as the specific conditions recited above.

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In one embodiment, the antagonist of chemokine receptor function is represented by Structural Formula (I):



(I)

5 and physiologically acceptable salts thereof.

Z is a cycloalkyl or non-aromatic heterocyclic ring group fused to one, two or more aromatic rings, wherein each ring in Z is independently substituted or unsubstituted.

10 n is an integer, such as an integer from one to about four. Preferably, n is one, two or three. More preferably n is two. In alternative embodiments, other aliphatic or aromatic spacer groups (L) can be employed for $(CH_2)_n$.

M is $>NR^2$ or $>CR^1R^2$. M is preferably $>C(OH)R^2$.

15 R¹ is -H, -OH, -N₃, a halogen, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)- (aliphatic group), -O-C(O)- (substituted aliphatic group), -C(O)O-(aliphatic group),

20 -C(O)O-(substituted aliphatic group), -COOH, -CN, -CO-NR³R⁴, -NR³R⁴; or R¹ can be a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M. R¹ is preferably -H or -OH.

-10-

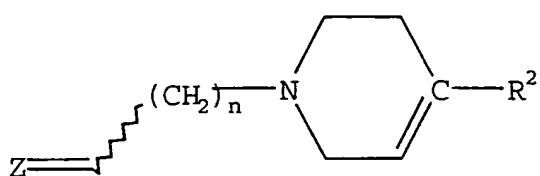
R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic

- 5 heterocyclic group or a substituted non-aromatic heterocyclic group. R^2 is preferably an aromatic group or a substituted aromatic group.

R^3 , R^4 , R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted 10 aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group.

- 15 R^1 and R^2 , R^3 and R^4 , or R^5 and R^6 taken together with the atom to which they are bonded, can alternatively form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

In embodiments where M is $>CR^1R^2$ and R^1 is a covalent bond between the carbon atom at M and an adjacent carbon 20 atom in the ring which contains M, the antagonist of chemokine function can be represented by Structural Formula (Ia).

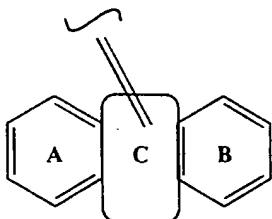


(Ia)

- 25 Z, n and R^2 are as described in Structural Formula (I).

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In one preferred embodiment, Z is a tricyclic ring system comprising two carbocyclic aromatic groups fused to a six, seven or eight membered cycloalkyl group or to a non-aromatic heterocyclic ring. In one example, Z is
5 represented by Structural Formula (II):



10

(II)

The phenyl rings in Structural Formula (II), labeled with an "A" and "B", are referred to herein as "Ring A" and "Ring B", respectively. The central ring, labeled with a "C", is referred to as "Ring C" and can be, for example, a
15 six, seven or eight membered non-aromatic carbocyclic ring (e.g., a cycloheptane or cyclooctane ring) or a non-aromatic heterocyclic ring. When Ring C is a non-aromatic heterocyclic ring, it can contain one or two heteroatoms such as nitrogen, sulfur or oxygen. When Z is represented
20 by Structural Formula (II), the tricyclic ring system can be connected to the remainder of the molecule by a covalent double bond between a carbon atom in Ring C and the carbon atom which, as depicted in Structural Formula (I), is bonded to Z.

25 Ring A and/or Ring B in Structural Formula (II) can be unsubstituted. Alternatively, Ring A and/or Ring B can

-12-

have one or more substituents. Suitable substituents are as described hereinbelow. In one example, Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or 5 $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$.

u is zero or one.

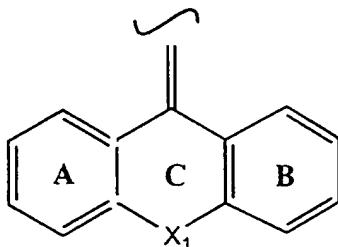
t is an integer, such as an integer from zero to about three, and the methylene group $-(CH_2)_t-$ can be substituted or unsubstituted.

10 R^{20} , R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group. Alternatively, R^{21} and R^{22} , taken together with the nitrogen atom to which they are bonded, can form a non-15 aromatic heterocyclic ring.

Ring C optionally contains one or more substituents, as described hereinbelow.

Examples of suitable tricyclic ring systems, Z, are provided by Structural Formula (III):

20



(III)

-13-

Ring A and Ring B in Structural Formula (III) are as described for Structural Formula (II).

X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-, -O-CH₂-,
-CH₂-O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂-, -CH₂-SO-,
5 -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO- or -CO-NR_c-.

Preferably X₁ is -CH₂-O-, -CH₂-CH₂-, -CH₂-S-, -NR_c-CO- or -CO-NR_c-.

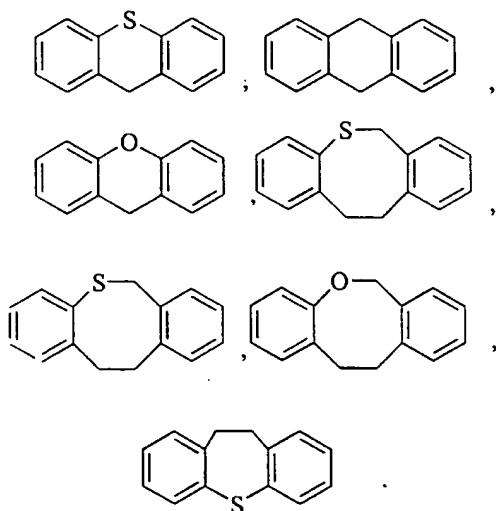
R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group.

In one example, R_c is -(CH₂)_s-COOR³⁰, -(CH₂)_s-C(O)-NR³¹R³² or -(CH₂)_s-NHC(O)-O-R³⁰, wherein s is an integer, such as an integer from one to about three;

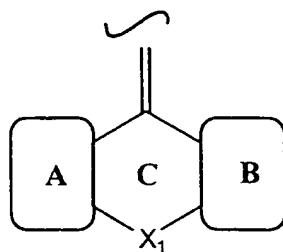
15 R³⁰, R³¹ and R³² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group. Alternatively, R³¹ and R³², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

20 Other examples of suitable tricyclic ring systems for Z include benzodiazepines, benzoazepines, benzoxazines, phenothiazines and groups represented by the following structural formulas:

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In another preferred embodiment, Z is a tricyclic ring system comprising two aromatic groups fused to a seven or eight membered cycloalkyl group or to a non-aromatic heterocyclic ring, wherein at least one of the aromatic groups is a heteroaryl group. In one example, Z is represented by Structural Formula (IV):



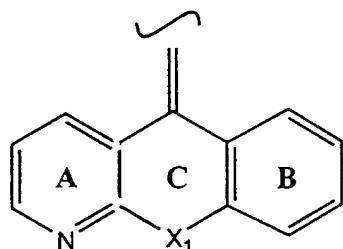
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Ring A in Structural Formula (IV) can be a substituted or unsubstituted heteroaryl group. Ring B in Structural Formula (IV) can be a substituted or unsubstituted aromatic group, e.g., a heteroaryl group or carbocyclic aryl group.

5 Suitable substituents are as described hereinbelow. In one example, Ring A and/or Ring B is substituted with - (O)_u-(CH₂)_t-C(O)OR²⁰, - (O)_u-(CH₂)_t-OC(O)R²⁰, - (O)_u-(CH₂)_t-C(O)-NR²¹R²² or - (O)_u-(CH₂)_t-NHC(O)O-R²⁰ as described above. u, t, R²⁰, R²¹, and R²² are as described 10 above. X₁ and R_c can be as described above for Structural Formula (III).

In another embodiment of the present invention Z is represented by Structural Formula (IV), wherein Ring A is a pyridyl group and Ring B is an aromatic or heteroaromatic 15 group. In this embodiment Ring A and Ring B are independently substituted or unsubstituted, and Ring B is preferably a phenyl group. X₁ and R_c can be as described above for Structural Formula (III).

In another embodiment of the present invention Z is 20 represented by Structural Formula (V):

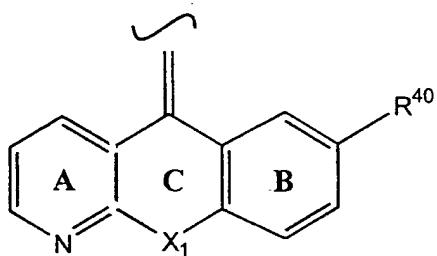


(V)

-16-

Ring A and Ring B can be independently substituted or unsubstituted as described above in Structural Formula (II), and X₁ can be as described above for Structural Formula (III).

- 5 In a preferred embodiment, Ring B in Structural Formula (V) is substituted para to the carbon atom of Ring B which is bonded to X₁ of Ring C, and Z is represented by Structural Formula (VI) :

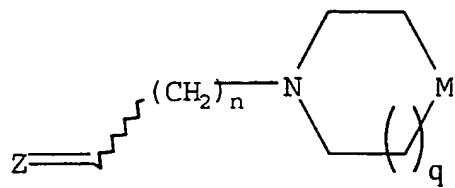


(VI)

- 10 X₁ can be as described above in Structural Formula (II). Preferably X₁ is -CH₂-O-, -CH₂-CH₂- or -CH₂-S-. R⁴⁰ is a substituent as described hereinbelow. Preferably R⁴⁰ is an aliphatic group, substituted aliphatic group, -O-(aliphatic group) or -O-(substituted aliphatic group). More preferably R⁴⁰ is an -O-alkyl, such as -O-CH₃, -O-C₂H₅, -O-C₃H₇ or -O-C₄H₉.

In another embodiment, the antagonist of chemokine activity can be represented by Structural Formula (VII) :

-17-



(VII)

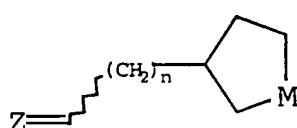
and physiologically acceptable salts thereof.

n and M are as described in Structural Formula (I).

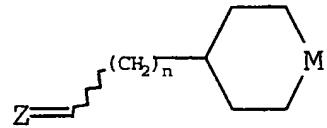
5 Z is as described herein, preferably as described in Structural Formula (V) or (VI).

q is an integer, such as an integer from zero to about three, and the ring containing M can be substituted or unsubstituted.

10 Thus, the antagonist of chemokine function can be represented by, for example, Structural Formulas (VIIa) - (VIId) :



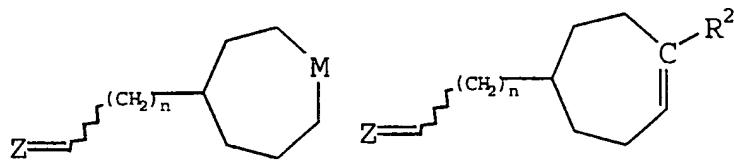
(VIIa)



(VIIb)

15

-18-



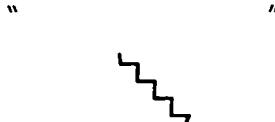
(VIIc)

(VIIId)

and physiologically acceptable salts thereof, wherein Z, n and M are as described in Structural Formula (VII), and the 5 ring which contains M is substituted or unsubstituted.

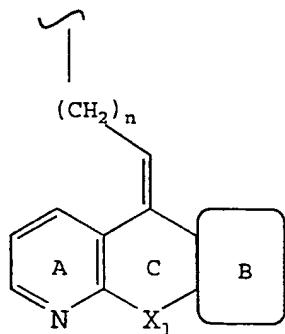
Another embodiment of the present invention includes novel compounds employed in these methods.

The compounds disclosed herein can be obtained as E- and Z-configurational isomers. It is expressly pointed out 10 that the invention includes compounds of the E- configuration and the Z-configuration around the double bond connecting Ring C of Z to the remainder of the molecule, and a method of treating a subject with compounds of the E-configuration, the Z-configuration, and mixtures 15 thereof. Accordingly, in the structural formulas presented herein, the symbol:



is used to represent both the E-configuration and the Z- 20 configuration. Preferably Ring A and the alkylene chain bonded to Ring C are in the cis configuration. For example, the compounds can have the configuration of:

-19-



It is understood that one configuration can have greater activity than another. The desired configuration
5 can be determined by screening for activity, employing the methods described herein.

Additionally, certain compounds of the invention may be obtained as different stereoisomers (e.g., diastereomers and enantiomers). It is pointed out that the invention
10 includes all isomeric forms and racemic mixtures of the disclosed compounds and a method of treating a subject with both pure isomers and mixtures thereof, including racemic mixtures. Again, it is understood that one stereoisomer may be more active than another. The desired isomer can be
15 determined by screening.

Also included in the present invention are physiologically acceptable salts of the compounds represented by Structural Formulas (I) through (VIIId). Salts of compounds containing an amine or other basic group
20 can be obtained, for example, by reacting with a suitable organic or inorganic acid, such as hydrogen chloride, hydrogen bromide, acetic acid, citric acid, perchloric acid

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and the like. Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Salts of compounds containing a carboxylic acid or other acidic 5 functional group can be prepared by reacting with a suitable base, for example, a hydroxide base. Salts of acidic functional groups contain a countercation such as sodium, potassium, ammonium, calcium and the like.

As used herein, aliphatic groups include straight 10 chained, branched or cyclic C₁-C₂₀ hydrocarbons which are completely saturated or which contain one or more units of unsaturation. For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic C₁-C₂₀ alkyl, alkenyl or alkynyl groups.

15 Aromatic groups include carbocyclic aromatic groups such as phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl, and heterocyclic aromatic or heteroaryl groups such as N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 5-tetrazolyl, 2-oxazolyl, 4-oxazolyl and 5-oxazolyl. Where 20 these rings are fused, for example, to Ring C, the stated point of attachment can be either of the two fused bonds. 25

Aromatic groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other rings.

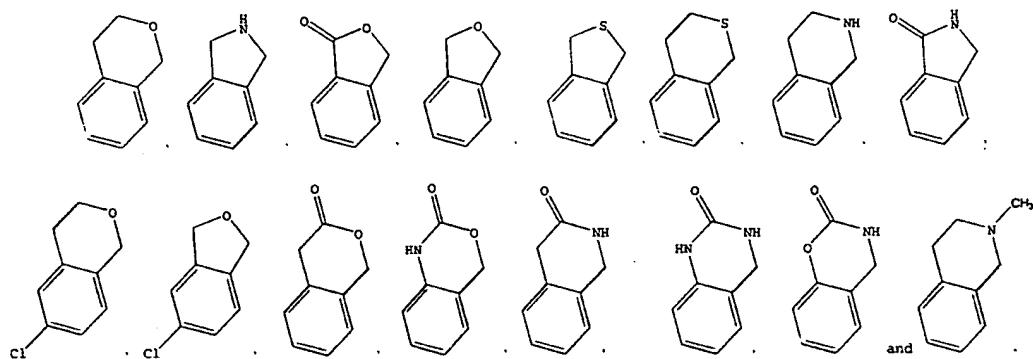
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Examples include tetrahydronaphthyl, 2-benzothienyl,
3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl,
3-indolyl, 2-quinolinyl, 3-quinolinyl, 2-benzothiazolyl,
2-benzooxazolyl, 2-benzimidazolyl, 2-quinolinyl, 3-
5 quinolinyl, 1-isoquinolinyl, 3-quinolinyl, 1-isoindolyl,
3-isoindolyl, acridinyl, 3-benzisoxazolyl, and the like.
Also included within the scope of the term "aromatic
group", as it is used herein, is a group in which one or
more carbocyclic aromatic rings and/or heteroaryl rings are
10 fused to a cycloalkyl or non-aromatic heterocyclic ring,
for example, benzocyclopentane, benzocyclohexane.

Non-aromatic heterocyclic rings are non-aromatic
carbocyclic rings which include one or more heteroatoms
such as nitrogen, oxygen or sulfur in the ring. The ring
15 can be five, six, seven or eight-membered and/or fused to
another ring, such as a cycloalkyl on aromatic ring.

Examples include 3-1H-benzimidazol-2-one, 3-1-alkyl-
benzimidazol-2-one, 3-1-methyl-benzimidazol-2-one,
2-tetrahydrofuranyl, 3-tetrahydrofuranyl,
20 2-tetrahyrothiophenyl, 3-tetrahyrothiophenyl, 2-morpholino,
3-morpholino, 4-morpholino, 2-thiomorpholino,
3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-
pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl,
1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl,
25 4-thiazolidinyl, diazolonyl, N-substituted diazolonyl, 1-
phthalimidyl, 1-3-alkyl-phthalimidyl, benzoxane,
benzopyrrolidine, benzopiperidine, benzoxolane,
benzothiolane, benzothiane,

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Suitable substituents on an aliphatic group, aromatic group (carbocyclic and heteroaryl), non-aromatic heterocyclic ring or benzyl group include, for example, an electron withdrawing group, a halogen, azido, -CN, -COOH, -OH, -CONR²⁴R²⁵, -NR²⁴R²⁵, -OS(O)₂NR²⁴R²⁵, -S(O)₂NR²⁴R²⁵, -SO₂H, -S(O)₂NH₂, guanidino, -(O)_u-(CH₂)_t-C(O)OR²⁰, -(O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²¹R²², -(O)_u-(CH₂)_t-NHC(O)O-R²⁰, -Q-H, -Q-(aliphatic group), 10 -Q-(substituted aliphatic group), -Q-(aryl), -Q-(aromatic group), -Q-(substituted aromatic group), -Q-(CH₂)_p-(substituted or unsubstituted aromatic group) (p is an integer from 1-5), -Q-(non-aromatic heterocyclic group) or -Q-(CH₂)_p-(non-aromatic heterocyclic group).

15 R²⁰, R²¹ or R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -NHC(O)-O-(aliphatic group), -NHC(O)-O-(aromatic group) or -NHC(O)-O-(non-aromatic heterocyclic group) and

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wherein R²¹ and R²², taken together with the nitrogen atom to which they are bonded, can form a non-aromatic heterocyclic ring.

t is an integer from zero to about three, and the 5 methylene group, -(CH₂)_t-, can be substituted or unsubstituted.

u is zero or one.

Q is -O-, -S-, -S(O)-, -S(O)₂-, -OS(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, 10 -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²³)-, -C(NR²³)NHNH-, -NHNHC(NR²³)-, -NR²⁴C(O)- or -NR²⁴S(O)₂-.

R²³ is -H, an aliphatic group, a benzyl group, an aryl group or non-aromatic heterocyclic group.

15 R²⁴ and R²⁵ are independently -H, -OH, an aliphatic group, a substituted aliphatic group, a benzyl group, an aryl group or non-aromatic heterocyclic group.

A substituted non-aromatic heterocyclic ring, benzyl group or aromatic group can also have an aliphatic or 20 substituted aliphatic group, as a substituent. A substituted aliphatic group can also have an oxo group, epoxy group, non-aromatic heterocyclic ring, benzyl group, substituted benzyl group, aromatic group or substituted aromatic group as a substituent. A substituted non- 25 aromatic heterocyclic ring can also have =O, =S, =NH or =N(aliphatic, aromatic or substituted aromatic group) as a substituent. A substituted aliphatic, substituted aromatic, substituted non-aromatic heterocyclic ring or

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substituted benzyl group can have more than one substituent.

Acyl groups include substituted and unsubstituted aliphatic carbonyl, aromatic carbonyl, aliphatic sulfonyl 5 and aromatic sulfonyl.

Suitable electron withdrawing groups include, for example, alkylimines, alkylsulfonyl, carboxamido, carboxylic alkyl esters, -CH=NH, -CN, -NO₂ and halogens.

In the structural formulas depicted herein, the single 10 or double bond by which a chemical group or moiety is connected to the remainder of the molecule or compound is indicated by the following symbol:



For example, the corresponding symbol in Structural 15 Formulas (II), (III) and (IV) indicates the double bond by which the central ring of the tricyclic ring system is connected to the remainder of the molecule represented by Structural Formula (I).

A "subject" is preferably a bird or mammal, such as a 20 human, but can also be an animal in need of veterinary treatment, e.g., domestic animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, fowl, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

25 An "effective amount" of a compound is an amount which results in the inhibition of one or more processes mediated

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by the binding of a chemokine to a receptor in a subject with a disease associated with aberrant leukocyte recruitment and/or activation. Examples of such processes include leukocyte migration, integrin activation, transient increases in the concentration of intracellular free calcium $[Ca^{2+}]_i$, and granule release of proinflammatory mediators. Alternatively, an "effective amount" of a compound is a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in the prevention of or a decrease in the symptoms associated with a disease associated with aberrant leukocyte recruitment and/or activation.

The amount of compound administered to the individual will depend on the type and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type of disease. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. Typically, an effective amount of the compound can range from about 0.1 mg per day to about 100 mg per day for an adult. Preferably, the dosage ranges from about 1 mg per day to about 100 mg per day. An antagonist of chemokine receptor function can also be administered in combination with one or more additional therapeutic agents, e.g. theophylline, β -adrenergic bronchodilators, corticosteroids, antihistamines, antiallergic agents, immunosuppressive agents (e.g., cyclosporin A, FK-506, prednisone, methylprednisolone) and the like.

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The compound can be administered by any suitable route, including, for example, orally in capsules, suspensions or tablets or by parenteral administration. Parenteral administration can include, for example, systemic
5 administration, such as by intramuscular, intravenous, subcutaneous, or intraperitoneal injection. The compound can also be administered orally (e.g., dietary), transdermally, topically, by inhalation (e.g., intrabronchial, intranasal; oral inhalation or intranasal
10 drops), or rectally, depending on the disease or condition to be treated. Oral or parenteral administration are preferred modes of administration.

The compound can be administered to the individual in conjunction with an acceptable pharmaceutical or
15 physiological carrier as part of a pharmaceutical composition for treatment of HIV infection, inflammatory disease, or the other diseases discussed above.
Formulation of a compound to be administered will vary according to the route of administration selected (e.g.,
20 solution, emulsion, capsule). Suitable carriers may contain inert ingredients which do not interact with the compound. Standard pharmaceutical formulation techniques can be employed, such as those described in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton,
25 PA. Suitable carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Methods for

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encapsulating compositions (such as in a coating of hard gelatin or cyclodextran) are known in the art (Baker, et al., "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).

5 The activity of compounds of the present invention can be assessed using suitable assays, such as receptor binding assays and chemotaxis assays. For example, as described in the Exemplification Section, small molecule antagonists of RANTES and MIP-1 α binding have been identified utilizing
10 THP-1 cells which bind RANTES and chemotax in response to RANTES and MIP-1 α as a model for leukocyte chemotaxis. Specifically, a high through-put receptor binding assay, which monitors 125 I-RANTES and 125 I-MIP-1 α binding to THP-1 cell membranes, was used to identify small molecule
15 antagonists which block binding of RANTES and MIP-1 α . Compounds of the present invention can also be identified by virtue of their ability to inhibit the activation steps triggered by binding of a chemokine to its receptor, such as chemotaxis, integrin activation and granule mediator
20 release. They can also be identified by virtue of their ability to block RANTES and MIP-1 α mediated HL-60, T-cell, peripheral blood mononuclear cell, and eosinophil chemotactic response.

The compounds disclosed herein can be prepared
25 accordingly to the schemes shown in Figures 1 - 5 and 7. The schemes are described in greater detail below.

Figure 1 shows the preparation of compounds represented by Structural Formula (I). L¹ is PPh₃Cl, PPh₃Br, PPh₃I or (EtO)₂P(O), L² is a suitable leaving group such as halogen,

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p-toluene sulfonate, mesylate, alkoxy, and phenoxy; Pg is a suitable protecting group such as tetrahydropyranyl; and the other symbols are as defined above.

In Step 1 of Figure 1, a Wittig reaction is carried out in a solvent such as ether, or tetrahydrofuran (THF) in the presence of a base such as sodium hydride, n-butyl lithium or lithium diisopropylamide (LDA) at 0°C up to the reflux temperature for the solvent used for 5 minutes to 72 h. Compounds represented by Formula II in Figure 1 can be prepared by methods disclosed in JP 61/152673, U.S. Patent 5089496, WO 89/10369, WO 92/20681 and WO 93/02081, the entire teachings of which are incorporated herein by reference.

In Step 2 of Figure 1, deprotection is carried out with an acid in a solvent such as methanol at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h. Alternatively, a compound of represented by Formula V in Figure 1 can be prepared directly from step 1 without isolating an intermediate. The reaction mixture obtained after the work up of the reaction described in step 1 can be dissolved in the solvent and reacted with the acid.

In Step 3 of Figure 1, the hydroxy group can be converted to a leaving group by known methods. Compounds represented by Formula VI in Figure 1 can be prepared by methods disclosed in J. Med. Chem., 1992 (35) 2074-2084 and JP 61/152673.

In Step 4 of Figure 1, an alkylation reaction is carried out in a solvent such as acetone, methyl ethyl

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ketone, ethyl acetate, toluene, tetrahydrofuran (THF) or dimethylformamide (DMF) in the presence of a base such as potassium carbonate or sodium hydride and a catalyst such as an alkali metal iodide at room temperature up to the
5 reflux temperature for the solvent used for 5 minutes to 72 h.

Figure 2 shows the preparation of compounds represented by Compound (VI-b). In Step 1 of Figure 2, a Grignard reaction may be carried out in a solvent such as
10 ether, or tetrahydrofuran (THF) at 0°C up to the reflux temperature for the solvent used for 5 minuets to 72 h. Compound VII is available commercially.

In Step 2 of Figure 2, bromination may be carried out with brominate agents such as hydrobromic acid,
15 bromotrimethylsilane or boron tribromide-methyl sulfide complex in a solvent such as acetic acid, dichloromethane or dichloroethane at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Figure 3 shows the preparation of compounds
20 represented by Structural Formula (I). In Figure 3, a reductive amination may be carried out with reducing regents such as sodium cyanoborohydride, sodium acetoxyborohydride or sodium borohydride in a solvent such as methanol, ethanol, tetrahydrofuran (THF),
25 dichloromethane or dichloroethane at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Figure 4 shows the preparation of compounds represented by Structural Formula (I), where in Z is

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represented by Structural Formulas (III) and wherein Ring A and/or Ring B in Z is substituted with R⁴⁰. In Figure 4, the alkylation reaction can be carried out in a solvent such as acetone, methyl ethyl ketone, ethyl acetate, 5 toluene, tetrahydrofuran (THF) or dimethylformamide (DMF) in the presence of a base such as potassium carbonate or sodium hydride and a catalyst such as an alkali metal iodide at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

10 Figure 5 is a schematic showing the preparation of the compounds represented by Structural Formula (I), wherein Z is represented by Structural Formulas (III) and wherein Ring A and/or Ring B in Z is substituted with - (O)_u - (CH₂)_t - COOR²⁰, - (O)_u - (CH₂)_t - OC(O)R²⁰, 15 - (O)_u - (CH₂)_t - C(O) - NR²¹R²² or - (O)_u - (CH₂)_t - NHC(O)O-R²⁰. In Figure 5, the hydrolysis reaction may be carried out in a mixture of aqueous alkali metal hydroxide solution and a solvent such as methanol, ethanol, tetrahydrofuran (THF) or dioxane at room temperature up to the reflux temperature 20 for the solvent used for 5 minutes to 72 h. The acylation reaction can be carried out using dicyclohexylcarbodiimide (DCC) or (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (DEC) in a solvent such as tetrahydrofuran (THF), dimethylformamide (DMF) or methylene chloride in the 25 presence of a base such as pyridine or triethylamine (when necessary) at temperatures of 0 to 100°C for 5 minutes to 72 h.

Figure 7 shows the preparation of compounds represented by Structural Formula (I), wherein Z is

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represented by Structural Formulas (III) and wherein Ring A or Ring B in Z is substituted with R⁴⁰. L4 is a suitable leaving group such as halogen or trifluoromethylsulfonate.

In Figure 7, a palladium coupling reaction such as
5 Stille coupling, Suzuki coupling, Heck reaction, or carboxylation using carbon monoxide may be carried out using a palladium catalyst such as tetrakis(triphenylphosphine)palladium, bis(triphenylphosphine)palladium chloride, and palladium acetate in a solvent such as tetrahydrofuran (THF), 1,4-dioxane, toluene, dimethylformamide (DMF), or 10 dimethylsulfoxide (DMSO) in the presence of additive (when necessary) such as triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, triethylamine, sodium bicarbonate, tetraethylammonium chloride, or lithium 15 chloride at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Compounds represented by Structural Formula (I), wherein Z is represented by Structural Formulas (III) or 20 (IV), X is -CO-NR_c- and R_c is -(CH₂)_s-COOR³⁰, -(CH₂)_s-C(O)-NR³¹R³² or -(CH₂)_s-NHC(O)-O-R³⁰, can be prepared by suitable modification of the scheme shown in Figure 1-5 and 7. One modification utilizes the starting material shown in Figure 1, wherein X is -CO-NH-. The amide is then alkylated with 25 L³-(CH₂)_s-COOR³⁰, wherein L³ is a suitable leaving group, using the alkylation procedures described above. The remainder of the synthesis is as described in Figures 1 - 5 and 7.

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Although Figures 1 - 5 and 7 show the preparation of compounds in which Rings A and B are phenyl rings, analogous compounds with heteroaryl groups for Rings A and B can be prepared by using starting materials with 5 heteroaryl groups in the corresponding positions. These starting materials can be prepared according to methods disclosed in JP 61/152673, U.S. Patent 5089496, WO 89/10369, WO 92/20681 and WO 93/02081.

The invention is illustrated by the following 10 examples which are not intended to be limiting in any way.

EXEMPLIFICATION

Example 1 - 4-(4-Chlorophenyl)-1-[3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)propyl]piperidin-4-ol

To a solution of 5-(3-bromopropylidene)-

15 10,11-dihydro-5H-dibenzo[a,d]cycloheptene (described in JP 48-030064) (200mg) in DMF (10ml) were added 4-(4-chlorophenyl)-4-hydroxypiperidine (230mg), potassium carbonate (360mg), and potassium iodide (50mg). The mixture was stirred at 70°C for 24 hours. Water and ethyl acetate were added to the reaction mixture, the organic 20 layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting 25 with ethyl acetate-hexane (1:1) to give the titled compound (250mg). $^1\text{H-NMR}$ (CDCl_3) δ : 1.65-2.11(5H, m), 2.32-3.10(8H, m), 3.22-3.67(4H, m), 5.87(1H, t), 7.03-7.44(12H, m). MS m/z: 444 (M+1).

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Example 2 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-6,11-dihydrodibenz[b,e]oxepine. $^1\text{H-NMR}$ (CDCl_3) δ : 1.61-2.16(5H,m), 2.37-2.80(8H,m), 5.22(2H,brs), 5.70(0.6x1H,t), 6.03(0.4x1H,t), 6.73-6.90(2H,m), 7.09-7.45(10H,m). MS m/z: 446 (M+1)

Example 3 - Membrane Preparations for Chemokine Binding and Binding Assays

Membranes were prepared from THP-1 cells (ATCC #TIB202). Cells were harvested by centrifugation, washed twice with PBS (phosphate-buffered saline), and the cell pellets were frozen at -70 to -85°C. The frozen pellet was thawed in ice-cold lysis buffer consisting of 5 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethane-sulfonic acid) pH 7.5, 2 mM EDTA (ethylenediaminetetraacetic acid), 5 $\mu\text{g/ml}$ each aprotinin, leupeptin, and chymostatin (protease inhibitors), and 100 $\mu\text{g/ml}$ PMSF (phenyl methane sulfonyl fluoride - also a protease inhibitor), at a concentration of 1 to 5×10^7 cells/ml. This procedure results in cell lysis. The suspension was mixed well to resuspend all of the frozen cell pellet. Nuclei and cell debris were removed by centrifugation of 400 x g for 10 minutes at 4°C. The supernatant was transferred to a fresh tube and the membrane fragments were collected by centrifugation at

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25,000 x g for 30 minutes at 4°C. The supernatant was aspirated and the pellet was resuspended in freezing buffer consisting of 10 mM HEPES pH 7.5, 300 mM sucrose, 1 μ g/ml each aprotinin, leupeptin, and chymostatin, and 10 μ g/ml PMSF (approximately 0.1 ml per each 10⁸ cells). All clumps were resolved using a minihomogenizer, and the total protein concentration was determined using a protein assay kit (Bio-Rad, Hercules, CA, cat #500-0002). The membrane solution was then aliquoted and frozen at -70 to -85°C until needed.

Binding Assays utilized the membranes described above. Membrane protein (2 to 20 μ g total membrane protein) was incubated with 0.1 to 0.2 nM ¹²⁵I-labeled RANTES or MIP-1 α with or without unlabeled competitor (RANTES or MIP-1 α) or various concentrations of compounds. The binding reactions were performed in 60 to 100 μ l of a binding buffer consisting of 10 mM HEPES pH 7.2, 1 mM CaCl₂, 5 mM MgCl₂, and 0.5% BSA (bovine serum albumin), for 60 min at room temperature. The binding reactions were terminated by harvesting the membranes by rapid filtration through glass fiber filters (GF/B or GF/C, Packard) which were presoaked in 0.3% polyethyleneimine. The filters were rinsed with approximately 600 μ l of binding buffer containing 0.5 M NaCl, dried, and the amount of bound radioactivity was determined by scintillation counting in a Topcount beta-plate counter.

The activities of test compounds are reported in the Table below as IC₅₀ values or the inhibitor concentration

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required for 50% inhibition of specific binding in receptor binding assays using ^{125}I -RANTES or $^{125}\text{MIP-1}\alpha$ as ligand and THP-1 cell membranes. Specific binding is defined as the total binding minus the non-specific binding; non-specific binding is the amount of cpm still detected in the presence of excess unlabeled Rantes or $^{125}\text{MIP-1}\alpha$.

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Table
BIOLOGICAL DATA

<u>Example</u>	<u>IC₅₀ (μM)</u>
5	1 <1
	2 <1
	8 <1
	12 <1
	17 <10
10	18 <1
	19 <1
	21 <1
	22 <1
	23 <1
	24 <10
15	25 <1
	26 <1
	27 <1
	28 <1
	29 <1
20	30 <1
	31 <1
	32 <1
	33 <1
	34 <1
25	35 <1
	36 <1
	38 <1
	39 <10
	40 <1
30	41 <1
	42 <1
	43 <10
	44 <1
	45 <1
35	46 <1
	47 <1
	48 <1
	49 <1

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BIOLOGICAL DATA (cont.)

Example	<u>IC₅₀ (μM)</u>
52	<1
53	<1
5	54 <1
	55 <1
	56 <1
	57 <10
10	59 <1
	60 <1
	61 <10
	62 <10
	63 <10
	64 <1
15	65 <1
	66 <1000
	67 <1
	68 <10
	69 <1
20	71 <1
	72 <10
	73 <10
	74 <1000
	75 <10
25	76 <10
	77 <1
	78 <1
	79 <1
	83 <1000
30	85 <1
	86 >10
	89 >10
	90 <1
	91 <1
35	111 <1
	114 <1
	117 <1
	118 <1
	128 <1
40	130 <1

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BIOLOGICAL DATA (cont.)

Example	IC ₅₀ (μ M)
131	<1
132	<1
5 133	<1
134	<1
135	<1
138	<1
139	<1
10 140	>10
141	<1
142	<10
143	<1
144	<1
15 145	<10
146	>10
147	<10
148	<10
149	<1000
20 150	<10
151	<1
152	<1
153	<1
154	<1
25 155	<1
158	<1
159	<1
160	<1
161	<10
30 162	<1
163	<1
166	<10
167	>1
168	1
35 173	<1
174	<1
175	<1
176	<1
178	<1
40 181	<1

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BIOLOGICAL DATA (cont.)

	<u>Example</u>	<u>IC₅₀ (μM)</u>
	182	<1
	183	<1
5	184	<10
	185	<1000
	186	<1
	187	<1
10	188	>10
	190	>10
	191	>10
	192	>10
	193	<1
	194	<1
15	195	<10
	197	<1
	199	<1
	248	<10

Example 8 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-
20 dibenz[b,e]thiepin-11-ylidene)propyl]piperidin-4-ol

Step 1

11-(3-Bromopropylidene)-6,11-dihydrodibenz[b,e]thiepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one with 6,11-dihydrodibenz[b,e]thiepin-11-one.

¹H-NMR (CDCl₃) δ: 2.50-2.64 (2H, m), 3.36-3.47 (3H, m), 4.99 (1H, d), 5.94 (1H, t), 6.98-7.31 (8H, m).

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Step 2

The titled compound was prepared by following the procedure of example 45, step 3 but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.65-1.80 (3H, m), 1.95-2.70 (10H, m), 3.35 (1H, d), 4.98 (1H, d), 5.96 (1H, t), 7.09-7.43 (12H, m).
MS m/z: 462 (M+1)

Example 12 - 1-[3-(5-Benzyl-6,11-dihydro-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

To a solution 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol hydrochloride (Example 39) (300mg) in DMF (5ml) were added sodium hydride (60% in oil, 200mg), benzyl bromide (0.15ml) and the mixture was stirred at room temperature for 1 hour. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate to give the titled compound (180mg).

¹H-NMR (CDCl₃) δ: 1.62-1.67 (2H, m), 1.99-2.20 (3H, m), 2.33-2.65 (8H, m), 5.10 (1H, d), 5.75 (1H, d), 5.94 (1H, t), 7.11-7.42 (16H, m), 7.91 (1H, dd).
MS m/z: 549 (M+1)

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Example 17 - 1-[3-(5-Carboxymethyl-6,11-dihydro-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-ethoxycarbonylmethyl-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol (Example 18) (1.0g) was solved in 1M hydrogen chloride in diethyl ether and stirred at room temperature for 24 hours. Aqueous sodium hydroxide and ethyl acetate were added to the reaction mixture, the aqueous layer was separated and neutralized with dilute hydrochloric acid. The precipitation was filtered to give the titled compound (250mg).

¹H-NMR (DMSO-d₆) δ: 1.44-1.61(2H,m), 2.07-2.17(1H,m), 2.35-3.01(9H,m), 4.28(1H,d), 4.59(1H,d), 5.83(1H,t), 7.18-

7.71(12H,m).

MS m/z: 517(M+1)

Example 18 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-ethoxycarbonylmethyl-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-5-ethoxycarbonylmethyl-6-oxo-5H-dibenz[b,e]azepine.

¹H-NMR (CDCl₃) δ: 1.30(3H,t), 1.64-1.69(2H,m), 1.97-2.10(3H,m), 2.38-2.71(8H,m), 4.27(2H,q), 4.32(1H,d), 4.84(1H,d), 5.88(1H,t), 7.16-7.45(11H,m), 7.88(1H,dd).

MS m/z: 545(M+1)

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Example 19 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-methyl-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
5 procedure of Example 1, but replacing
5-(3-bromopropylidene)-10,11-dihydro-5H-
dibenzo[a,d]cycloheptene with
11-(3-bromopropylidene)-5-methyl-6-oxo-5H-
dibenzo[b,e]azepin.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.58-2.06 (5H, m), 2.39-2.75 (8H, m),
3.53 (3H, s), 5.84 (1H, t), 7.10-7.44 (11H, m), 7.85-7.89 (1H, m).
MS m/z: 473 (M+1).

Example 21 - 4-(4-Chlorophenyl)-1-[3-(5H-dibenzo[a,d]cycloheptene-5-ylidene)propyl]piperidin-4-ol

15 The titled compound was prepared by following the
procedure of example 1, but replacing 5-(3-
bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene
with 5-(3-bromopropylidene)-5H-dibenzo[a,d]cycloheptene.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.58-1.63 (2H, m), 2.00-2.05 (2H, m), 2.26-
2.46 (6H, m), 2.62-2.66 (2H, m), 5.55 (1H, t), 6.85 (2H, s), 7.24-
7.40 (12H, m).
MS m/z: 442 (M+1).

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Example 22 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-methoxycarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
5 procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-6,11-dihydro-2-methoxycarbonyldibenz[b,e]oxepine.

¹H-NMR (CDCl₃) δ: 1.65-1.70 (2H, m), 2.01-2.13 (3H, m), 2.41-
10 2.80 (7H, m), 3.85 (3H, s), 5.40 (2H, brs), 5.73 (0.6x1H, t),
6.09 (0.4x1H, t), 6.76 (0.6x1H, d), 6.82 (0.4x1H, d), 7.21-
7.43 (8H, m), 7.73 (1H, dd), 7.87 (0.6x1H, d), 7.97 (0.4x1H, d).
MS m/z: 504 (M+1).

Example 23 - 1-[3-(2-Butoxycarbonyl-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the
procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene
20 with 11-(3-bromopropylidene)-2-butoxy-6,11-dihydrodibenz[b,e]oxepine.

¹H-NMR (CDCl₃) δ: 0.96 (3H, t), 1.53 (2H, q), 1.70-1.77 (3H, m),
2.02-2.14 (3H, m), 2.39-2.78 (5H, m), 4.27 (2H, t), 5.27 (2H, brs),
5.75 (0.8x1H, t), 6.10 (0.2x1H, t), 6.78 (1H, d), 7.27-
25 7.43 (8H, m), 7.76 (1H, dd), 7.89 (0.8x1H, d), 7.98 (0.2x1H, d).
MS m/z: 546 (M+1).

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Example 24 - 1-[3-(2-Carboxyl-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

- To a solution of 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-methoxycarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (Example 22) (100mg) in ethanol (3ml) were added 15% sodium hydroxide aqueous solution (0.6ml) and the mixture was heated to reflux for 12 hours. The solvent was distilled off under reduced pressure. Water and ethyl acetate were added to the reaction mixture, the aqueous layer was separated and neutralized with dilute hydrochloric acid. The precipitation was filtered to give the titled compound (80mg).
- 15 $^1\text{H-NMR}$ (CD_3OD) δ : 1.73-1.79 (2H,m), 2.14-2.19 (2H,m), 2.80-2.93 (3H,m), 3.02-3.11 (3H,m), 3.24-3.29 (2H,m), 5.25 (2H,brs), 5.61 (0.7x1H,t), 6.05 (0.3x1H,t), 6.72 (1H,d), 7.22-7.40 (8H,m), 7.52-7.65 (1H,m), 7.75 (0.7x1H,d), 7.80 (0.3x1H,d).
- 20 MS m/z: 490 (M+1).

Example 25 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-dimethylaminocarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

- The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-2-dimethylaminocarbonyl-6,11-dihydrodibenz[b,e]oxepine.

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¹H-NMR (CDCl₃) δ: 1.62-1.67 (2H, m), 2.00-2.12 (2H, m), 2.37-2.47 (8H, m), 2.89 (6H, s), 5.25 (2H, brs), 5.68 (0.7x1H, t), 6.03 (0.3x1H, t), 6.71 (0.3x1H, d), 6.78 (0.7x1H, d), 7.13-7.40 (10H, m).

5 MS m/z: 517 (M+1).

Example 26 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-hydroxymethyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

To a solution of (4-chlorophenyl)-1-[3-(6,11-dihydromethoxycarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (110mg) in THF (8ml) were added lithium aluminum hydride (1.0M, 0.42ml) dropwise at 0 °C, and the mixture was stirred at room temperature for 1 hour. Aqueous sodium hydroxide (1M) was added to the reaction mixture to stir for 30 minutes, then ethyl acetate and brine was added to the mixture. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with dichloromethane-methanol (10:1) to give the titled compound (90mg).

¹H-NMR (CDCl₃) δ: 1.61-1.66 (2H, m), 1.98-2.03 (2H, m), 2.39-2.48 (3H, m), 2.57-2.79 (6H, m), 4.52 (2H, s), 5.20 (2H, brs), 5.66 (0.8x1H, t), 6.01 (0.2x1H, t), 6.67 (0.2x1H, d), 6.79 (0.8x1H, d), 7.06 (1H, dd), 7.15-7.37 (9H, m).

MS m/z: 476 (M+1).

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Example 27 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-(1-hydroxy-1-methyl)ethyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-methoxycarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (60mg) in THF (6ml) were added methylmagnesium chloride (3.0M, 0.16ml) dropwise at 0 °C, and the mixture was stirred at room temperature for 2 hour, the reaction mixture was quenched by saturated ammonium aqueous, then ethyl acetate and water was added to the mixture. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (95:5) to give the titled compound (20mg).

¹H-NMR (CDCl₃) δ: 1.54(0.7x6H,s), 1.62(0.3x6H,s), 1.63-1.70(2H,m), 2.03-2.10(3H,m), 2.38-2.49 (3H,m), 2.62-2.82(4H,m), 5.17(2H,brs), 5.68(0.7x1H,t), 6.05(0.3x1H,t), 6.75(0.3x1H,d), 6.83(0.7x1H,d), 7.18-7.43(10H,m).
MS m/z: 504 (M+1).

Example 28 - 4-(4-Chlorophenyl)-1-[3-(2-cyano-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-2-cyano-6,11-dihydrodibenz[b,e]oxepine.

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¹H-NMR (CDCl₃) δ: 1.67-1.72 (2H, m), 2.02-2.13 (2H, m), 2.37-2.77 (8H, m), 5.35 (2H, brs), 5.75 (0.7x1H, t), 6.07 (0.3x1H, t), 6.78 (0.3x1H, d), 6.82 (0.7x1H, d), 7.25-7.51 (10H, m).
MS m/z: 471 (M+1).

5 Example 29 - 1-[3-(2-Aminomethyl-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(2-cyano-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (380mg) in EtOH (20ml) were added Raney nickel (50% slurry in water, 60 mg), and the mixture was hydrogenated at 15 psi for 2 hours. The mixture was filtered through the celite and distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with dichloromethane-methanol-aqueous ammonium (95:5:1) to give the titled compound (130mg).

10 ¹H-NMR (CDCl₃) δ: 1.76-1.94 (3H, m), 2.18-2.34 (2H, m), 2.85-3.10 (8H, m), 3.88 (2H, s), 5.30 (2H, brs), 5.59 (1H, t), 6.78 (1H, d), 7.13-7.40 (10H, m).
20 MS m/z: 475 (M+1).

Example 30 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-nitrodibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-6,11-dihydro-2-nitrodibenz[b,e]oxepine.

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¹H-NMR (CDCl₃) δ: 1.62-1.67 (2H,m), 1.80-2.12 (3H,m), 2.28-2.78 (8H,m), 5.05 (0.3x2H,brs), 5.40 (0.7x2H,brs), 5.90 (0.7x1H,t), 6.17 (0.3x1H,t), 6.82 (0.3x1H,d), 6.92 (0.7x1H), 7.28-7.41 (8H,m), 7.82 (1H,dd), 8.15 (0.7x1H,d),
5 8.22 (0.3x1H,d).
MS m/z: 491 (M+1).

Example 31 - 1-[3-(2-Amino-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-nitrodibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (120mg) in EtOH (15ml) were added tin (II) chloride (190mg), and the mixture was heated to reflux for 1 hour. The was distilled off under reduced pressure. The residue was added ethyl acetate and sodium aqueous to neutralize. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with dichloromethane-methanol (95:5)
20 to give the titled compound (70mg).

¹H-NMR (DMSO-d₆) δ: 1.54-1.60 (2H,m), 1.85-2.00 (2H,m), 2.30-2.80 (8H,m), 3.88 (2H,s), 5.07 (2H,brs), 5.66 (1H,t), 6.41-6.46 (2H,m), 6.59 (1H,d), 7.24-7.49 (8H,m).

MS m/z: 461 (M+1).

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Example 32 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-hydroxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol
Step 1

- 11-(3-Bromopropylidene)-6,11-dihydro-2-hydroxydibenz[b,e]oxepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one with 6,11-dihydro-2-hydroxydibenz[b,e]oxepin-11-one.
- ¹H-NMR (CDCl₃) δ: 2.69(2H,q), 3.39 (2H,t), 5.20(2H,brs), 5.92(1H,t), 6.50-6.81(4H,m), 7.17-7.37(4H,m).

Step 2

- The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.60-1.75(3H,m), 1.95-2.10(2H,m), 2.35-2.80(8H,m), 5.10(2H,brs), 5.93(1H,t), 6.56(2H,brs), 6.71(1H,brs), 7.11-7.35(8H,m).

MS m/z: 462 (M+1)

- Example 33 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-methoxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol
Step 1

- 11-(3-Bromopropylidene)-6,11-dihydro-2-methoxydibenz[b,e]oxepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one with 6,11-dihydro-2-methoxydibenz[b,e]oxepin-11-one.

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¹H-NMR (CDCl₃) δ: 2.74(2H,q), 3.43 (2H,t), 3.77(3H,s), 5.10(2H,brs), 6.02(1H,t), 6.70-6.83(3H,m), 7.21-7.38(4H,m).

Step 2

The titled compound was prepared by following the
5 procedure of example 45, step 3, but replacing 5-(3-
bromopropylidene)-10,11-dihydro-5H-dibenzo [a,d] cycloheptene
with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.59-1.65(2H,m), 1.95-2.66(11H,m),
3.75(3H,s), 5.10(2H,brs), 6.03(1H,t), 6.69(2H,brs),
10 6.82(1H,brs), 7.20-7.40(8H,m).

MS m/z: 476 (M+1)

Example 34 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-ethoxydibenz [b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-
15 2-hydroxydibenz [b,e]oxepin-11-ylidene)propyl]piperidin-4-ol
(Example 32) (200mg) in DMF (5ml) were added sodium hydride
(60% in oil, 25mg), ethyl iodide (0.052ml) and the mixture
was stirred at room temperature for 1 hour. Water and
ethyl acetate were added to the reaction mixture, the
20 organic layer was separated and washed with saturated
aqueous sodium chloride, and dried with magnesium sulfate.
The solvent was distilled off under reduced pressure. The
residue was purified by silica gel chromatography eluting
with ethyl acetate-hexane (1:1) to give the titled compound
25 (170mg).

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¹H-NMR (CDCl₃) δ: 1.37 (3H, t), 1.60-1.65 (2H, m), 1.95-2.08 (3H, m), 2.28-7.5 (8H, m), 3.96 (2H, q), 5.15 (2H, brs), 6.02 (1H, t), 6.68 (2H, brs), 6.82 (1H, brs), 7.19-7.42 (8H, m).
MS m/z: 490 (M+1)

5 Example 35 - 1-[3-(3-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

3-Bromo-11-(3-bromopropylidene)-6,11-dihydrodibenz[b,e]oxepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one with 3-bromo-6,11-dihydrodibenz[b,e]oxepin-11-one.

¹H-NMR (CDCl₃) δ: 2.74 (2H, q), 3.43 (2H, t), 3.77 (3H, s), 5.10 (2H, brs), 6.02 (1H, t), 6.70-6.83 (3H, m), 7.21-7.38 (4H, m).

15 Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with the product of step 1.

20 ¹H-NMR (CDCl₃) δ: 1.63-1.70 (3H, m), 1.96-2.10 (2H, m), 2.32-2.69 (8H, m), 5.20 (2H, brs), 6.00 (1H, t), 6.92-7.00 (2H, m), 7.11-7.14 (1H, m), 7.24-7.42 (8H, m).

MS m/z: 524, 526 (M+1)

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Example 36 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-methoxypiperidine

To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-methoxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (Example 2) (400mg) in DMF (5ml) were added sodium hydride (60% in oil, 50mg), methyl iodide (0.07ml) and the mixture was stirred at room temperature for 1 hour. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:1) to give the titled compound (100mg).

¹H-NMR (CDCl₃) δ: 1.90-2.04 (4H,m), 2.34-2.62 (8H,m), 2.93 (3H,s), 5.25 (2H,brs), 6.04 (1H,t), 6.75-6.91 (3H,m), 7.09-7.37 (9H,m).

MS m/z: 460 (M+1)

Example 37 - 4-Acetoxy-4-(4-chlorophenyl)-1-[3-(6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]piperidine

To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-methoxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (Example 2) (200mg) in dichloromethane (5ml) were added acetyl chloride (0.06ml), triethylamine (0.19ml) and the mixture was stirred at room temperature for 1 hour. Aqueous sodium bicarbonate and ethyl acetate were added to the reaction mixture, the

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organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting 5 with ethyl acetate-hexane (1:4) to give the titled compound (190mg).

¹H-NMR (CDCl₃) δ: 1.98-2.85(12H,m), 2.02(3H,s), 2.93(3H,s), 5.23(2H,brs), 6.01(1H,t), 6.73-6.90(3H,m), 7.11-7.40(9H,m). MS m/z: 488 (M+1)

10 Example 38 - 1-[3-(8-Bromo-4,10-dihydrothieno[3,2-c][1]benzoxepin-10-ylidene)propyl]piperidin-4-(4-chlorophenyl)-4-ol

Step 1

15 8-Bromo-10-(3-bromopropylidene)-4,10-dihydrothieno[3,2-c][1]benzoxepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one with 4,10-dihydrothieno[3,2-c][1]benzoxepin-10-one.

1¹H-NMR (CDCl₃) δ: 2.84(2H,q), 3.45(2H,t), 5.10(2H,s), 6.11(1H,t), 6.65(1H,d), 7.03-7.08(2H,m), 7.38-7.43(2H,m).

Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene 25 with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.66-1.75(3H,m), 2.03-2.16(2H,m), 2.40-2.86(8H,m), 5.09(0.7x2H,s), 5.14(0.3x2H,s), 5.90(0.3x1H,t),

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6.10 (0.7x1H, t), 6.64 (0.7x1H, d), 6.75 (0.3x1H, d),
6.90 (0.3x1H, d), 7.03-7.09 (2H, m), 7.21-7.45 (6H, m).
MS m/z: 532 (M+1)

Example 39 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-6-oxo-
5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol

Step 1

11-(3-Bromopropylidene)-6,11-dihydro-6-oxo-5H-
dibenz[b,e]azepine was prepared by following the procedure
of example 45, step 1 and 2, but replacing 5,11-dihydro-7-
methoxypyrido[2,3-c] [1]benzoxepin-5-one with 6,11-dihydro-
6-5H-dibenz[b,e]azepin-6,11-dione.

¹H-NMR (CDCl₃) δ: 2.70-2.92 (2H, m), 3.45 (2H, t), 5.92 (1H, t),
7.08-7.58 (7H, m), 8.05 (1H, dd), 9.00 (1H, brs).

Step 2

The titled compound was prepared by following the
procedure of example 45, step 3, but replacing 5-(3-
bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene
with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.61-1.66 (2H, m), 1.97-2.20 (3H, m), 2.35-
2.68 (8H, m), 5.80 (1H, t), 7.03-7.53 (11H, m), 8.02 (1H, dd),
9.27 (1H, brs).

MS m/z: 459 (M+1)

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Example 40 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-ethyl-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 12, but replacing benzyl bromide with 5 ethyl iodide.

¹H-NMR (CDCl₃) δ: 1.19-1.28 (3H,m), 1.63-1.69 (2H,m), 1.99-2.16 (3H,m), 2.37-2.70 (8H,m), 3.77-3.85 (1H,m), 4.40-4.48 (1H,m), 5.85 (1H,t), 7.12-7.45 (11H,m), 7.85 (1H,dd).

MS m/z: 487 (M+1)

10 Example 41 - 1-[3-(5-n-Butyl-6,11-dihydro-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

The titled compound was prepared by following the procedure of example 12, but replacing benzyl bromide with 15 n-butyl iodide.

¹H-NMR (CDCl₃) δ: 0.90-0.98 (3H,m), 1.25-2.20 (9H,m), 2.40-2.87 (8H,m), 3.62-3.72 (1H,m), 4.52-4.64 (1H,m), 5.85 (1H,t), 7.16-7.45 (11H,m), 7.88 (1H,dd).

MS m/z: 515 (M+1)

20 Example 42 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-(3-hydroxypropyl)-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol

To a solution 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol 25 hydrochloride (Example 39) (500mg) in DMF (8ml) were added sodium hydride (60% in oil, 200mg), 2-(3-bromopropoxy)tetrahydro-2H-pyran (0.5ml) and the mixture

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was stirred at room temperature for 6 hours. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate.

- 5 The solvent was distilled off under reduced pressure. The residue was solved in 1M hydrogen chloride in diehyl ether and stirred at room temperature for 1 hour. Aqueous sodium bicarbonate and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with
10 saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate to give the titled compound (250mg).

15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.25-2.87(15H,m), 3.51-3.56(2H,m), 3.76-
3.82(1H,m), 4.81-4.87(1H,m), 5.86(1H,t), 7.16-7.45(11H,m),
7.82(1H,dd).

MS m/z: 517 (M+1)

Example 43 - 1-[3-(5-tert-Butoxycarbonylmethyl-6,11-dihydro-
20 6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

The titled compound was prepared by following the procedure of example 12, but replacing benzyl bromide with tert-butyl bromoacetate.

25 $^1\text{H-NMR}$ (CDCl_3) δ : 1.50(9H,s), 1.65-1.70(2H,m), 1.95-
2.10(3H,m), 2.42-2.75(8H,m), 4.24(1H,d), 4.75(1H,d),
5.88(1H,t), 7.16-7.46(11H,m), 7.90(1H,dd).

MS m/z: 573 (M+1)

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Example 44 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1

5 To a solution of the product of example 45, step 1 (4.3g) in dichloroethane (100ml) was added boron tribromide-methyl sulfide complex (19.3g) and the mixture was heated to reflux for 3 hour. Water and ethyl acetate were added to the reaction mixture and neutralized with 10 dilute NaOH solution. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:2) to 15 give 5-(3-bromopropylidene)-5,11-dihydro-7-hydroxy [1]benzoxepino[2,3-b]pyridine (3.2g).

¹H-NMR (CDCl₃) δ: 2.72(2H,q), 3.45(2H,t), 5.28(2H,brs), 6.03(1H,t), 6.66-6.80(3H,m), 7.26(1H,dd), 7.58(1H,dd), 8.51(1H,dd).

20 Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-5,11-dihydro-7-methoxy [1]benzoxepino[2,3-b]pyridine with the product of step 1.

25 ¹H-NMR (DMSO-d₆) δ: 1.46-1.51(2H,m), 1.74-1.85(2H,m), 2.29-2.51(8H,m), 5.15(2H,brs), 6.07(1H,t), 6.61-6.70(3H,m), 7.33-7.48(5H,m), 7.73(1H,dd), 8.47(1H,dd), 9.06(1H,s).

MS m/z: 463 (M+1)

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Example 45 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1

5 To a solution of 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one (5.0g) in THF (50ml) was added 1.1M cyclopropylmagnesium bromide THF solution (25ml) at 0°C. The reaction mixture was warmed to room temperature, and stirred for 30 minutes. Aqueous ammonium chloride and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was filtered and washed with ethyl acetate-hexane (1:2) to give 5-cyclopropyl-5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ol (5.0g).

Step 2

To a solution of the product of step 1 (4.3g) in acetic acid (30ml) was added 48% aqueous HBr (25ml) at 20 10°C. The reaction mixture was warmed to room temperature, and stirred for 12 hours. Water and ethyl acetate were added to the reaction mixture and neutralized with dilute NaOH solution. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried over 25 magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:4) to

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give 5-(3-bromopropylidene)-5,11-dihydro-7-methoxy
[1]benzoxepino[2,3-b]pyridine (5.6g).

¹H-NMR (CDCl₃) δ: 2.74 (2H, q), 3.46 (2H, t), 3.78 (3H, s),
5.25 (2H, brs), 6.07 (1H, t), 6.72-6.82 (3H, m), 7.21-7.42 (5H, m),
5 7.56 (1H, dd), 8.45 (1H, dd).

Step 3

To a solution the product of step 2 (1.1g) in DMF (15ml) were added 4-(4-chlorophenyl)-4-hydroxypiperidine (0.81g) and potassium carbonate (0.53g) and the mixture was
10 stirred at room temperature for 3 hours. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The
15 residue was purified by silica gel chromatography eluting with methylene chloride-methanol (10:1) to give the titled compound as major regioisomer (0.86g) and minor one (0.05g).

Major isomer

20 ¹H-NMR (CDCl₃) δ: 1.64-1.69 (2H, m), 1.91-2.08 (3H, m), 2.34-
2.69 (8H, m), 3.77 (3H, s), 5.25 (2H, brs), 6.07 (1H, t), 6.72-
6.82 (3H, m), 7.21-7.42 (5H, m), 7.56 (1H, dd), 8.45 (1H, dd).

MS m/z: 477 (M+1)

Minor isomer

25 ¹H-NMR (CDCl₃) δ: 1.65-1.79 (3H, m), 2.01-2.13 (2H, m), 2.35-
2.76 (8H, m), 3.76 (3H, s), 5.22 (2H, brs), 5.95 (1H, t), 6.72-
6.80 (2H, m), 7.06 (1H, d), 7.16 (1H, dd), 7.28 (2H, d),
7.42 (2H, d), 7.66 (1H, dd), 8.39 (1H, dd).

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MS m/z: 477 (M+1)

Example 46 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

5 The titled compound was prepared by following the procedure of example 34, but replacing 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-hydroxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol with 4-(4-chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol (example 44).

¹H-NMR (CDCl₃) δ: 1.38 (3H, t), 1.67-1.72 (3H, m), 2.05-2.16 (2H, m), 2.40-2.80 (8H, m), 3.99 (2H, q), 5.26 (2H, brs), 6.05 (1H, t), 6.71-6.82 (3H, m), 7.23-7.43 (5H, m), 7.57 (1H, dd), 8.47 (1H, dd).

15 MS m/z: 491 (M+1)

Example 47 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-isopropoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

20 The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with isopropyl bromide.

¹H-NMR (CDCl₃) δ: 1.30 (6H, d), 1.60-1.70 (3H, m), 1.99-2.09 (2H, m), 2.33-2.69 (8H, m), 4.37-4.48 (1H, m), 5.26 (2H, brs), 6.06 (1H, t), 6.73-6.82 (3H, m), 7.21-7.43 (5H, m), 7.55 (1H, dd), 25 8.47 (1H, dd).

MS m/z: 505 (M+1)

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Example 48 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethoxycarbonylmethyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
5 procedure of example 46, but replacing ethyl iodide with
ethyl bromoacetate.

¹H-NMR (CDCl₃) δ: 1.28(3H,t), 1.63-1.68(2H,m), 1.97-
2.02(3H,m), 2.33-2.68(8H,m), 4.24(2H,q), 4.55(2H,s),
5.26(2H,brs), 6.06(1H,t), 6.73-6.88(3H,m), 7.21-7.42(5H,m),
10 7.55(1H,dd), 8.44(1H,dd).

MS m/z: 549 (M+1)

Example 49 - 4-(4-Chlorophenyl)-1-[3-(7-cyanomethyloxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

15 The titled compound was prepared by following the
procedure of example 46, but replacing ethyl iodide with
bromoacetonitrile.

¹H-NMR (CDCl₃) δ: 1.62-1.67(2H,m), 1.94-2.06(2H,m),
2.21(1H,brs), 2.34-2.66(8H,m), 4.70(2H,s), 5.26(2H,brs),
20 6.10(1H,t), 6.80(2H,brs), 6.92(1H,brs), 7.22-7.41(5H,m),
7.56(1H,dd), 8.44(1H,dd).

MS m/z: 502 (M+1)

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Example 50 - 1-[3-(7-(2-Acetoxyethyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the
5 procedure of example 46, but replacing ethyl iodide with 2-bromoethyl acetate.

¹H-NMR (CDCl₃) δ: 1.65-1.72 (3H, m), 1.97-2.09 (5H, m), 2.37-
2.70 (8H, m), 4.11-4.14 (2H, m), 4.37-4.41 (2H, m), 5.25 (2H, brs),
6.07 (1H, t), 6.75-6.84 (3H, m), 7.23-7.43 (5H, m), 7.56 (1H, dd),
10 8.47 (1H, dd).

MS m/z: 549 (M+1)

Example 51 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-hydroxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

15 To a solution of 1-[3-(7-(2-acetoxyethyl)oxy-5,11-[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol (Example 50) (140mg) in ethanol (5ml) were added 15% sodium hydroxide aqueous solution (2ml) and the mixture was heated to reflux for 1 hour.

20 Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting
25 with methylene chloride-methanol (10:1) to give the titled compound (120mg).

¹H-NMR (CDCl₃) δ: 1.64-1.69 (2H, m), 1.98-2.10 (3H, m), 2.36-
2.79 (8H, m), 3.89-3.94 (2H, m), 3.99-4.04 (2H, m), 5.24 (2H, brs),

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6.04 (1H, t), 6.71-6.84 (3H, m), 7.23-7.41 (5H, m), 7.54 (1H, dd),
8.43 (1H, dd).

MS m/z: 507 (M+1)

Example 52 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-morpholinoethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with 4-(2-chloroethyl)morpholine hydrochloride.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.62-1.67 (2H, m), 1.95-2.08 (2H, m), 2.20-2.67 (13H, m), 2.74 (2H, t), 3.67-3.71 (4H, m), 4.04 (2H, t), 5.23 (2H, brs), 6.05 (1H, t), 6.73-6.82 (3H, m), 7.20-7.41 (5H, m), 7.53 (1H, dd), 8.42 (1H, dd).

MS m/z: 576 (M+1)

15 Example 53 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1

5-(3-Bromopropylidene)-5,11-dihydro [1]benzoxepino[2,3-b]pyridine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-one.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 2.71 (2H, q), 3.46 (2H, t), 5.33 (2H, brs), 6.04 (1H, t), 7.01-7.17 (3H, m), 7.29 (1H, dd), 7.56 (1H, dd), 8.53 (1H, dd).

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Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-5,11-dihydro-7-methoxy

- 5 [1]benzoxepino[2,3-b]pyridine with the product of step 1.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.66-1.71(2H,m), 2.00-2.20(3H,m), 2.36-2.69(8H,m), 5.34(2H,brs), 6.10(1H,t), 6.83-6.96(3H,m), 7.17-7.44(6H,m), 7.60(1H,dd), 8.46(1H,dd).

MS m/z: 447 (M+1)

- 10 Example 54 - 1-[3-(8-Bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

8-Bromo-5-(3-bromopropylidene)-5,11-

- 15 dihydro[1]benzoxepino[2,3-b]pyridine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 8-bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-one.

- 20 $^1\text{H-NMR}$ (CDCl_3) δ : 2.75(2H,q), 3.50(2H,t), 5.38(2H,brs), 6.08(1H,t), 6.85-6.98(2H,m), 7.18-7.35(3H,m), 7.59(1H,dd), 8.54(1H,dd).

Step 2

- The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridine with the product of step 1.

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¹H-NMR (CDCl₃) δ: 1.64-1.69 (2H,m), 1.90-2.07 (3H,m), 2.30-2.67 (8H,m), 5.30 (2H,brs), 6.08 (1H,t), 7.00-7.07 (2H,m), 7.13 (1H,d), 7.25-7.42 (5H,m), 7.56 (1H,dd), 8.47 (1H,dd).
MS m/z: 525, 527 (M+1)

5 Example 55 - 4-(4-Chlorophenyl)-1-[3-(10,11-dihydro-10-oxo-5H-pyrido[2,3-c][2]benzazepin-5-ylidene)propyl]piperidin-4-ol

Step 1

5-(3-Bromopropylidene)-10,11-dihydro-10-oxo-5H-pyrido[2,3-c][2]benzazepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 10,11-dihydro-5H-pyrido[2,3-c][2]benzazepin-5,10-dione.
¹H-NMR (CDCl₃) δ: 2.75-2.90 (2H,m), 3.45 (2H,t), 5.92 (1H,t), 7.04-7.70 (5H,m), 8.10 (1H,dd), 8.48 (1H,dd), 10.00 (1H,brs).

Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.64-1.69 (3H,m), 2.00-2.12 (2H,m), 2.35-2.70 (8H,m), 5.82 (1H,t), 7.08 (1H,dd), 7.23-7.62 (8H,m), 8.04 (1H,dd), 8.32 (1H,dd), 8.76 (1H,brs).

MS m/z: 460 (M+1)

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Example 56 - 4-(4-Chlorophenyl)-1-[3-(10,11-dihydro-11-methyl-10-oxo-5H-pyrido[2,3-c][2]benzazepin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 36, but replacing of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-methoxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol with 5-(3-bromopropylidene)-10,11-dihydro-10-oxo-5H-pyrido[2,3-c][2]benzazepine.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.64-1.70 (3H,m), 2.00-2.10 (2H,m), 2.41-2.69 (8H,m), 3.62 (3H,s), 5.82 (1H,t), 7.07 (1H,dd), 7.25-7.54 (8H,m), 7.91 (1H,dd), 8.34 (1H,dd).

MS m/z: 474 (M+1)

Example 57 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)ethyl]piperidin-4-ol

Step 1

To a solution of methyltriphenylphosphonium bromide (2.2g) in THF (20ml) was added 1.6M n-butyl lithium hexane solution (2.9ml) at 0°C for 30 minutes. To the reaction mixture cooled to 0°C was added 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one (1.0g) dropwise as THF solution (5ml), and the mixture was warmed to room temperature, and stirred for 3 hours. Aqueous ammonium chloride and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced

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pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:4) to give 5,11-dihydro-7-methoxy-5-methylenepyrido[2,3-c] [1]benzoxepine (0.14g).

5 Step 2

To a solution of DMF (0.54ml) was added phosphorus oxychloride (0.41ml) at 0°C for 10 minutes. To the reaction mixture was added the product of step 1 (210mg) in carbontetrachloride (5ml) and the mixture was heated to 10 reflux for 5 hours. Aqueous sodium bicarbonate and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The 15 residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:4) to give 3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)acetaldehyde (130mg).

¹H-NMR (CDCl₃) δ: 3.77(0.7x3H, s), 3.79(0.3x3H, s),
20 5.31(2H, s), 6.46(0.7x1H, d), 6.52(0.3x1H, d), 6.78-
7.40(4H, m), 7.68(0.3x1H, dd), 7.78(0.7x1H, dd),
8.55(0.7x1H, dd), 8.64(0.3x1H, dd), 9.62(0.3x1H, d),
9.79(0.7x1H, d).

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Step 3

The titled compound was prepared by following the procedure of example 58, step 2, but replacing of 3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propanaldehyde with product of step 2.

¹H-NMR (CDCl₃) δ: 1.64-1.82 (2H,m), 1.92-2.22 (3H,m), 2.43-2.58 (2H,m), 2.79-3.45 (6H,m), 3.68 (0.3x3H,s), 3.70 (0.7x3H,s), 5.24 (2H,brs), 6.18 (0.7x1H,t), 6.21 (0.3x1H,t), 6.72-7.42 (8H,m), 7.78 (0.3x1H,dd), 10 7.85 (0.7x1H,dd), 8.42 (0.7x1H,dd), 8.46 (0.3x1H,dd).
MS m/z: 463 (M+1).

Example 58 - 4-(4-Chlorophenyl)-1-[4-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)butyl]piperidin-4-ol

15 Step 1

3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propenaldehyde was prepared by following the procedure of example 57, step 2, but replacing 5,11-dihydro-7-methoxy-5-methylene[1]benzoxepino[2,3-b]pyridine with 5,11-dihydro-7-methoxy-5-(propyl-1-ene)[1]benzoxepino[2,3-b]pyridine (by-product of example 45, step 3).

¹H-NMR (CDCl₃) δ: 3.78 (0.3x3H,s), 3.80 (0.7x3H,s), 5.32 (2H,brs), 6.34-6.39 (1H,m), 6.72-7.38 (6H,m), 25 7.58 (0.7x1H,dd), 7.77 (0.3x1H,dd), 8.49 (0.3x1H,dd), 8.60 (0.7x1H,dd), 9.51 (0.7x1H,d), 9.54 (0.3x1H,d).

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Step 2

To a solution of the product of step 1 (90mg) in dichloromethane (6ml) were added sodium triacetoxyborohydride (170mg), 4-(4-chlorophenyl)-4-hydroxypiperidine (70mg) and acetic acid (0.02ml) and the mixture stirred at room temperature for 24 hour. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate.

10 The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with dichloromethane-methanol (95:5) to give 4-(4-chlorophenyl)-1-[4-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)buten-2-yl]piperidin-4-ol (110mg).

15 ¹H-NMR (CDCl₃) δ: 1.68-1.73 (2H,m), 2.04-2.16 (2H,m), 2.43-2.72 (3H,m), 2.77-2.81 (2H,m), 3.08-3.13 (2H,m), 3.73 (0.3x3H,s), 3.77 (0.7x3H,s), 5.20 (2H,brs), 5.98-6.05 (1H,m), 6.23-7.43 (10H,m), 7.58 (0.7x1H,dd), 7.65 (0.3x1H,dd), 8.37 (0.3x1H,dd), 8.45 (0.7x1H,dd).

20 MS m/z: 489 (M+1).

Step 3

To a solution of the product of step 2 (8mg) in ethanol (2ml) were added 10% Pd-C (2mg) was stirred under hydrogen (under a balloon) at room temperature for 1 hour. The mixture was filtered through the celite and distilled off under reduced pressure to give the titled compound (6mg).

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¹H-NMR (CDCl₃) δ: 1.68-3.00 (15H, m), 3.77 (3H, s), 5.18-5.35 (2H, m), 5.94 (0.4H, t, E isomer), 6.06 (0.6H, t, Z isomer), 6.65-6.88 (3H, m), 7.05-7.73 (6H, m), 8.30-8.56 (1H, m).
MS m/z: 491 (M+1)

5 Example 59 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-phenyl-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-phenyl-4-hydroxypiperidine.

10 ¹H-NMR (CDCl₃) δ: 1.68-1.73 (2H, m), 2.02-2.15 (3H, m), 2.38-2.72 (8H, m), 3.77 (3H, s), 5.26 (2H, brs), 6.08 (1H, t), 6.72-6.83 (3H, m), 7.21-7.36 (4H, m), 7.46-7.49 (2H, m), 7.58 (1H, dd), 15 8.46 (1H, dd).

MS m/z: 443 (M+1).

Example 60 - 4-(4-Bromophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

20 The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-bromophenyl)-4-hydroxypiperidine.

25 ¹H-NMR (CDCl₃) δ: 1.65-1.69 (2H, m), 2.00-2.10 (3H, m), 2.37-2.71 (8H, m), 3.76 (3H, s), 5.24 (2H, brs), 6.05 (1H, t), 6.70-6.82 (3H, m), 7.24 (1H, dd), 7.38 (2H, d), 7.44 (2H, s), 7.52 (1H, dd), 8.44 (1H, dd).

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MS m/z: 521,523 (M+1).

Example 61 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

5 The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.43-1.60 (2H,m), 1.80-1.98 (2H,m), 2.00-2.18 (3H,m), 2.34-2.48 (4H,m), 2.63-2.76 (2H,m), 3.64-3.73 (1H,m), 3.70 (3H,s), 5.35 (2H,brs), 6.06 (1H,t), 6.74-6.84 (3H,m), 7.25 (1H,dd), 7.60 (1H,dd), 8.50 (1H,dd).

MS m/z: 367 (M+1).

Example 62 - 4-Benzyl-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

15 The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 20 4-benzyl-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.42-1.57 (3H,m), 1.62-1.75 (2H,m), 2.22-2.70 (8H,m), 2.79 (2H,s), 3.80 (3H,s), 5.25 (2H,brs), 6.08 (1H,t), 6.73-6.84 (3H,m), 7.18-7.24 (6H,m), 7.57 (1H,dd), 8.50 (1H,dd).

25 MS m/z: 457 (M+1).

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Example 63 - 4-Cyano-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-phenylpiperidine

The titled compound was prepared by following the
5 procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-cyano-4-phenylpiperidine.

¹H-NMR (CDCl₃) δ: 1.97-2.06 (4H,m), 2.37-2.60 (6H,m), 2.85-
2.90 (2H,m), 3.79 (3H,s), 5.27 (2H,brs), 6.08 (1H,t), 6.72-
10 6.84 (3H,m), 7.24-7.58 (7H,m), 8.49 (1H,dd).
MS m/z: 452 (M+1).

Example 64 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-phenylpiperidine

15 The titled compound was prepared by following the
procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-phenylpiperidine.

¹H-NMR (CDCl₃) δ: 1.73-1.79 (4H,m), 1.96-2.03 (2H,m), 2.37-
20 2.52 (5H,m), 2.86-2.94 (2H,m), 3.77 (3H,s), 5.26 (2H,brs).
6.08 (1H,t), 6.72-6.83 (3H,m), 7.17-7.31 (6H,m), 7.56 (1H,dd),
8.49 (1H,dd).
MS m/z 426 (M+1).

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Example 65 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the
5 procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(4-chlorophenyl)piperidine.

¹H-NMR (CDCl₃) δ: 1.68-1.74 (4H, m), 1.96-2.03 (2H, m), 2.36-
2.48 (5H, m), 2.89-2.94 (2H, m), 3.77 (3H, s), 5.27 (2H, brs),
10 6.07 (1H, t), 6.73-6.83 (3H, m), 7.10-7.27 (5H, m), 7.57 (1H, dd),
8.48 (1H, dd).
MS m/z: 461 (M+1).

Example 66 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-piperidinopiperidine

The titled compound was prepared by following the
procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-piperidinopiperidine.

20 ¹H-NMR (CDCl₃) δ: 1.40-2.00 (12H, m), 2.15-2.60 (9H, m), 2.80-
2.92 (2H, m), 3.80 (3H, s), 5.28 (2H, brs), 6.05 (1H, t), 6.75-
6.86 (3H, m), 7.30 (1H, dd), 7.55 (1H, dd), 8.46 (1H, dd).
MS m/z 434 (M+1).

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Example 67 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-keto-1-benzimidazolinyl)piperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(2-keto-1-benzimidazolinyl)piperidine.

¹H-NMR (CDCl₃) δ: 1.75-1.79 (2H, m), 2.03-2.15 (2H, m), 2.38-2.52 (6H, m), 2.93-2.98 (2H, m), 3.78 (3H, s), 4.30-4.38 (1H, m), 5.30 (2H, brs), 6.10 (1H, t), 6.73-6.84 (3H, m), 7.01-7.03 (3H, m), 7.21-7.28 (2H, m), 7.59 (1H, dd), 8.48 (1H, dd).
MS m/z: 483 (M+1).

Example 68 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-keto-3-methyl-1-benzimidazolinyl)piperidine

The titled compound was prepared by following the procedure of example 36, but replacing of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-methoxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol with 1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-keto-1-benzimidazolinyl)piperidine.

¹H-NMR (CDCl₃) δ: 1.72-1.76 (2H, m), 2.09-2.14 (2H, m), 2.23-2.54 (6H, m), 2.91-2.96 (2H, m), 3.38 (3H, s), 3.77 (3H, s), 4.30-4.37 (1H, m), 5.27 (2H, brs), 6.08 (1H, t), 6.71-6.83 (3H, m), 6.93-7.06 (3H, m), 7.23-7.60 (2H, m), 8.08 (1H, dd), 8.48 (1H, dd).
MS m/z: 497 (M+1).

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Example 69 - 8-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one

The titled compound was prepared by following the
5 procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one.

¹H-NMR (CDCl₃) δ: 1.65-1.70 (2H,m), 2.36-2.41 (2H,m), 2.53-
2.79 (8H,m), 3.76 (3H, s), 4.70 (2H,s), 5.25 (2H,brs),
10 6.10 (1H,t), 6.71-6.88 (6H,m), 7.21-7.27 (3H,m), 7.58-
7.61 (2H,m), 8.48 (1H,dd).
MS m/z: 497 (M+1).

Example 70 - 4-Anilino-4-carbamyl-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the
procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-anilino-4-carbamylpiperidine.

20 ¹H-NMR (CDCl₃) δ: 1.85-1.90 (2H,m), 2.03-2.08 (2H,m), 2.19-
2.46 (6H,m), 2.62-2.67 (2H,m), 3.75 (3H,s), 3.97 (1H,brs),
5.27 (2H,brs), 5.53 (1H,brs), 6.03 (1H,t), 6.60 (2H,d), 6.70-
6.85 (4H,m), 7.12-7.25 (4H,m), 7.53 (1H,dd), 8.46 (1H,dd).
MS m/z 485 (M+1).

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Example 71 - 1-(4-Chlorophenyl)-4-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperazine

The titled compound was prepared by following the
5 procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
1-(4-chlorophenyl)piperazine.

¹H-NMR (CDCl₃) δ: 2.36-2.53 (8H, m), 3.07-3.09 (4H, m),
3.76 (3H, s), 5.26 (2H, brs), 6.08 (1H, t), 6.72-6.81 (5H, m),
10 7.16-7.28 (3H, m), 7.56 (1H, dd), 8.49 (1H, dd).
MS m/z: 462 (M+1).

Example 72 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-pyrimidyl)piperazine

15 The titled compound was prepared by following the
procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
1-(2-pyrimidyl)piperazine.

¹H-NMR (CDCl₃) δ: 2.37-2.53 (8H, m), 3.74-3.83 (7H, m),
20 5.27 (2H, brs), 6.08 (1H, t), 6.45 (1H, t), 6.72-6.83 (3H, m),
7.25 (1H, dd), 7.56 (1H, dd), 8.27 (2H, d), 8.49 (1H, dd).
MS m/z: 430 (M+1).

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Example 73 - 1-Cyclohexyl-4-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperazine

The titled compound was prepared by following the
5 procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
1-cyclohexylpiperazine.

¹H-NMR (CDCl₃) δ: 1.12-1.27 (6H, m), 1.74-1.86 (6H, m), 2.18-
2.52 (11H, m), 3.76 (3H, s), 5.26 (2H, brs), 6.04 (1H, t), 6.74-
10 6.81 (3H, m), 7.23 (1H, dd), 7.55 (1H, dd), 8.48 (1H, dd).
MS m/z: 434 (M+1).

Example 74 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-furoyl)piperazine

15 The titled compound was prepared by following the
procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
1-(2-furoyl)piperazine.

¹H-NMR (CDCl₃) δ: 2.34-2.48 (8H, m), 3.71-3.74 (7H, s),
20 5.24 (2H, brs), 6.05 (1H, t), 6.42 (1H, dd), 6.70-6.80 (3H, m),
6.93 (1H, d), 7.23 (1H, dd), 7.42 (1H, d), 7.53 (1H, dd),
8.46 (1H, dd).
MS m/z: 446 (M+1).

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Example 75 - 4-(3-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
5 procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(3-chlorophenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.61-1.75 (2H,m), 1.98 (1H,brs),
1.99 (2H,dt), 2.25 (3H,s), 2.30-2.76 (8H,m), 3.73 (3H,s),
10 5.22 (2H,brs), 5.95 (0.1H,t, E isomer), 6.04 (0.9H,t, Z
isomer), 6.71-6.89 (3H,m), 6.95 (1H,dd), 7.15-7.20 (0.3H,m, E
isomer), 7.21-7.35 (2.7H,m, Z isomer), 7.53 (0.9H,dd, Z
isomer), 7.65 (0.1H,dd, E isomer), 8.35 (0.1H,dd, E isomer),
8.45 (0.9H,dd, Z isomer).
15 MS m/z: 477 (M+1)

Example 76 - 4-(2-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
20 procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(2-chlorophenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.98-2.08 (2H,m), 2.24 (2H,dt), 2.38-
2.78 (9H,m), 3.77 (3H,s), 5.27 (2H,brs), 6.08 (1H,t), 6.82-
25 6.75 (3H,m), 7.28-7.19 (3H,m), 7.33 (1H,dd), 7.49 (1H,dd),
7.58 (1H,dd), 8.40 (0.1H,dd, Z isomer), 8.47 (0.9H,dd, E
isomer).

MS m/z: 477 (M+1)

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Example 77 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-fluorophenyl)piperidin-4-ol

The titled compound was prepared by following the
5 procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(4-fluorophenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.58-1.72 (2H, m), 2.04 (2H, dt), 2.22-
2.78 (9H, m), 3.75 (3H, s), 5.26 (2H, brs), 6.09 (1H, t), 6.70-
10 6.88 (3H, m), 7.00 (2H, dd), 7.23 (1H, dd), 7.42 (2H, dd),
7.56 (1H, dd), 8.41 (1H, dd).

MS m/z: 461 (M+1)

Example 78 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(p-tolyl)piperidin-4-ol

The titled compound was prepared by following the
procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(p-tolyl)-4-hydroxypiperidine.

20 ¹H-NMR (CDCl₃) δ: 1.65-1.78 (2H, m), 2.02 (2H, dt), 2.31 (3H, s),
2.24-2.75 (9H, m), 3.75 (3H, s), 5.25 (2H, brs), 6.07 (1H, t),
6.72-6.84 (3H, m), 7.13 (2H, d), 7.23 (1H, dd), 7.34 (1H, d),
7.56 (1H, dd), 8.43 (1H, dd).

MS m/z: 457 (M+1)

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Example 79 - 4-(3,4-Dichlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
5 procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(3,4-dichlorophenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.58-1.72 (2H,m), 1.84 (1H,brs),
2.02 (2H,td), 2.32-2.72 (8H,m), 3.76 (3H,s), 5.27 (2H,brs),
10 5.95 (0.1H,t, E isomer), 6.07 (0.9H,t, Z isomer), 6.72-6.85
(3H,M), 7.12-7.20 (0.2H,m, E isomer), 7.21-7.32 (0.18H,m, Z
isomer), 7.32-7.45 (1H,m), 7.52-7.56 (2H,m), 8.37 (0.9H,dd, E
isomer), 8.45 (0.1H,dd, Z isomer).

MS m/z: 512 (M+1)

15 Example 83 - 4-(5-Chloropyridin-2-yl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
procedure of example 45, step 3, but replacing

20 4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(5-chloropyridin-2-yl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.77-1.82 (2H,m), 2.36-2.94 (11H,m),
3.77 (3H,brs), 5.26 (2H,brs), 6.07 (1H,t), 6.76-6.84 (3H,m),
7.26 (1H,dd), 7.57 (1H,dd), 8.49-7.48 (1H,d), 8.42-

25 8.53 (3H,m).

MS m/z: 478 (M+1)

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Example 85 -4-(5-Chloro-2-keto-1-benzimidazolinyl)-
1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-
ylidene)propyl]piperidine

The titled compound was prepared by following the
5 procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(5-chloro-2-keto-1-benzimidazolinyl)piperidine.

¹H-NMR (CDCl₃) δ: 1.68-1.72(2H,m), 2.03-2.60(8H,m), 2.90-
3.02(2H,m), 3.78(3H,s), 4.32-4.21(1H,m), 5.29(2H,brs),
10 5.95(0.1H,t, E siomer), 6.08(0.9H,t, Z isomer), 6.70-
6.92(3H,m), 7.02(1H,dd), 7.08-7.20(1H,m), 7.26(1H,dd),
7.58(0.9H,dd, Z isomer), 7.70(0.1H,dd, E isomer),
8.42(0.1H,dd, E isomer), 8.48(0.9H,dd, Z isomer),
10.5(1H,s). (NH is not observed in the spectrum)
15 MS m/z: 517(M+1)

Example 86 - 4-(p-Chloroanilino)-1-[3-(5,11-dihydro-7-
methoxy[1]benzoxepino[2,3-b]pyridin-5-
ylidene)propyl]piperidine

The titled compound was prepared by following the
20 procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(p-chloroanilino)piperidine.

¹H-NMR (CDCl₃) δ: 1.20-1.54(2H,m), 1.85-2.20(4H,m), 2.24-
2.60(4H,m), 2.73(2H,m), 3.18(1H,m), 3.77(3H,s),
25 5.27(2H,brs), 6.06(1H,t), 6.47(2H,m), 6.68-6.90(3H,m),
7.07(2H,m), 7.24(1H,dd), 7.57(1H,m), 8.48(1H,dd). NH signal
was not observed.
MS m/z: 476(M+1)

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Example 89 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(p-tosyl)piperazine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-(p-tosyl)piperazine.

¹H-NMR (CDCl₃) δ: 2.20-2.54 (11H, m), 2.82-3.10 (4H, m), 3.73 (3H, s), 5.16 (2H, brs), 6.00 (1H, t), 6.66-6.85 (3H, m), 7.21 (1H, dd), 7.31 (2H, m), 7.51 (1H, dd), 7.61 (2H, m), 8.45 (1H, dd).

MS m/z: 506 (M+1)

Example 90 - 1'-(3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)spiro[isobenzofuran-1(3H),4'-piperidine]

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with spiro[isobenzofuran-1(3H),4'-piperidine].

¹H-NMR (CDCl₃) δ: 1.62-1.82 (2H, m), 1.92 (2H, dt), 2.25-2.85 (8H, m), 3.76 (3H, s), 5.03 (2H, s), 5.30 (2H, brs), 6.11 (1H, t), 6.68-6.90 (3H, m), 7.02-7.34 (5H, m), 7.58 (1H, dd), 8.48 (1H, dd).

MS m/z: 455 (M+1)

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Example 91 - 5-Chloro-1'-(3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)spiro[isobenzofuran-1(3H),4'-piperidine]

The titled compound was prepared by following the
5 procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
5-chlorospiro[isobenzofuran-1(3H),4'-piperidine].
1H-NMR (CDCl₃) δ: 1.69-1.74 (2H, m), 1.81-1.93 (2H, m),
2.30-2.44 (4H, m), 2.52-2.63 (2H, m), 2.71-2.75 (2H, m),
10 3.79 (3H, s), 5.00 (2H, s), 5.28 (2H, brs), 6.09 (1H, t),
6.73-6.84 (3H, m), 7.03 (1H, d), 7.17-7.28 (3H, m), 7.58 (1H, dd),
8.49 (1H, dd).
MS m/z: 489 (M+1)

Example 111 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro[1]benzothiepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
procedure of example 45, but replacing
5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one
20 with 5,11-dihydro[1]benzothiepino[2,3-b]pyridin-5-one.
1H-NMR (CDCl₃) δ: 1.66-1.78 (3H, m), 2.04-2.65 (10H, m),
3.66 (1H, brd), 5.05 (1H, brd), 6.03 (1H, t), 7.04-7.46 (10H, m),
8.44 (1H, dd).
MS m/z: 463 (M+1)

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Example 114 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-8-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
5 procedure of example 45, but replacing
5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one
with
5,11-dihydro-8-methoxy[1]benzoxepino[2,3-b]pyridin-5-one.
1H-NMR (CDCl₃) δ: 1.66-1.70 (3H, m), 1.98-2.09 (2H, m),
10 2.34-2.70 (8H, m), 3.75 (3H, s), 5.32 (2H, brs), 6.02 (1H, t),
6.39 (1H, d), 6.51 (1H, dd), 7.19-7.44 (6H, m), 7.57 (1H, dd),
8.49 (1H, dd).
MS m/z: 477 (M+1)

Example 115 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
procedure of example 45, but replacing
5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one
20 with
5,11-dihydro-7-methyl[1]benzoxepino[2,3-b]pyridin-5-one.
1H-NMR (CDCl₃) δ: 1.50 (1H, brs), 1.66-1.70 (2H, m),
1.98-2.10 (2H, m), 2.28 (3H, s), 2.34-2.42 (4H, m),
2.52-2.57 (2H, m), 2.66-2.70 (2H, m), 5.30 (2H, brs), 6.08 (1H, t),
25 6.76 (1H, d), 6.97 (1H, dd), 7.09 (1H, d), 7.24-7.44 (5H, m),
7.57 (1H, dd), 8.49 (1H, dd).
MS m/z: 461 (M+1)

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Example 117 - 1-[3-(7-Chloro-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with

7-chloro-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-one.

1H-NMR (CDCl₃) δ: 1.66-1.71(3H,m), 2.00-2.10(2H,m),
10 2.36-2.44(4H,m), 2.52-2.57(2H,m), 2.66-2.70(2H,m),
5.32(2H,brs), 6.13(1H,t), 6.78(1H,d), 7.11(1H,dd),
7.26-7.44(5H,m),
7.58(1H,dd), 8.51(1H,dd).

MS m/z: 481(M+1)

15 Example 118 - 1-[3-(7-Carboxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

A mixture of the product of example 169 (500 mg), potassium acetate (330 mg), palladium(II) diacetate (10 mg), 1,1'-bis(diphenylphosphino)ferrocene (93 mg), in dimethylsulfoxide (10 ml) was purged with carbon monoxide for 5 minutes and stirred under a carbon monoxide balloon at 60°C for 3 hours. Water was added to the reaction mixture, the precipitation was filtered. The solid were dissolved with ethyl acetate and dilute sodium hydroxide solution. The aqueous layer was separated and neutralized with dilute hydrochloric acid. The precipitation was filtered to give the titled compound (250 mg).

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1H-NMR (DMSO-d₆) δ: 1.45-1.55 (2H, m), 1.75-1.85 (2H, m),
2.36-2.62 (8H, m), 5.42 (2H, brs), 6.21 (1H, t), 6.90 (1H, d),
7.40-7.52 (5H, m), 7.75 (1H, dd), 7.83 (1H, dd),
7.95 (1H, d), 8.56 (1H, dd).

5 MS m/z: 491 (M+1)

Example 128 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-propoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
10 procedure of example 46, but replacing ethyl iodide with
propyl iodide.

1H-NMR (CDCl₃) δ: 1.03 (3H, t), 1.65-1.70 (2H, m), 1.78 (2H, q),
1.98-2.09 (3H, m), 2.37-2.45 (4H, m), 2.51-2.56 (2H, m),
2.66-2.70 (2H, m), 3.88 (2H, t), 5.26 (2H, brs), 6.08 (1H, t),
15 6.72-6.84 (3H, m), 7.23-7.43 (5H, m), 7.58 (1H, dd), 8.43 (1H, dd).
MS m/z: 505 (M+1)

Example 130 - 4-(4-Chlorophenyl)-1-[3-(7-cyclopropylmethoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

20 The titled compound was prepared by following the
procedure of example 46, but replacing ethyl iodide with
cyclopropylmethyl bromide.

¹H-NMR (CDCl₃) δ: 0.31-0.37 (2H, m), 0.60-0.67 (2H, m),
1.21-1.28 (1H, m), 1.66-1.72 (3H, m), 2.01-2.11 (2H, m),
25 2.37-2.71 (8H, m), 3.77 (2H, d), 5.27 (2H, brs), 6.08 (1H, t),
6.73-6.86 (3H, m), 7.23-7.44 (5H, m), 7.58 (1H, dd), 8.47 (1H, dd).
MS m/z: 517 (M+1)

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Example 131 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-dimethylaminoethyl)oxy)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with 2-(dimethylamino)ethyl chloride hydrochloride.

¹H-NMR (CDCl₃) δ: 1.71-1.76 (2H, m), 2.12-2.21 (2H, m), 2.38 (6H, s), 2.40-2.79 (11H, m), 4.07 (2H, t), 5.28 (2H, brs), 6.07 (1H, t), 6.74-6.86 (3H, m), 7.27-7.46 (5H, m), 7.59 (1H, dd), 8.49 (1H, dd).

MS m/z: 534 (M+1)

Example 132 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(tetrazol-5-yl)methoxy)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-triphenylmethyltetrazol-5-yl)methoxy)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol was prepared by following the procedure of example 46, but replacing ethyl iodide with

(2-triphenylmethyltetrazol-5-yl)methyl chloride.

¹H-NMR (CDCl₃) δ: 1.64-1.70 (3H, m), 2.02-2.15 (2H, m), 2.35-2.71 (8H, m), 5.29 (2H, brs), 5.33 (2H, s), 6.03 (1H, t), 6.77 (1H, d), 6.83 (1H, dd), 6.96 (1H, d), 7.04-7.08 (6H, m), 7.23-7.45 (14H, m), 7.54 (1H, dd), 8.50 (1H, dd).

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Step 2

A solution of the product of step 1 (530 mg) in acetone (2.5 ml), acetic acid (2.5 ml) and water (2.5 ml) was stirred at 55°C for 30 minutes. The reaction mixture 5 was distilled off under reduced pressure. The residue was washed with methanol to give the titled compound (280 mg).
¹H-NMR (DMSO-d₆) δ: 1.69-1.74 (2H, m), 1.99-2.09 (2H, m), 2.95-3.14 (8H, m), 5.18 (2H, brs), 5.20 (2H, s), 6.14 (1H, t), 6.76 (1H, d), 6.93 (1H, dd), 7.04 (1H, d), 7.39-7.48 (5H, m), 10 7.78 (1H, dd), 8.52 (1H, dd).

MS m/z: 545 (M+1)

Example 133 - 1-[3-(7-Carboxymethoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

15 To a solution of product of example 48 (3.0 g) in methanol (50 ml) was added 1N sodium hydroxide solution (8 ml) and the mixture stirred at room temperature for 1 hour. The reaction mixture was distilled off under reduced pressure. The residue was dissolved with water and 20 neutralized with 1N hydrochloric acid. The precipitation was filtered and washed with water to give the titled compound (2.6 g).

¹H-NMR (DMSO-d₆) δ: 1.48-1.53 (2H, m), 1.76-1.88 (2H, m), 2.32-2.60 (8H, m), 4.60 (2H, s), 5.18 (2H, brs), 6.16 (1H, t), 25 6.72-6.84 (3H, m), 7.34-7.48 (5H, m), 7.73 (1H, dd), 8.50 (1H, dd).
MS m/z: 521 (M+1)

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Example 134 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-dimethylaminocarbonylmethyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of product of example 133 (420 mg) in
5 dimethylformamide (17 ml) were added 1-hydroxybenzotriazol
hydrate (250 mg), 1-(3-dimethylaminopropyl)-3-
ethylcarbodiimide hydrochloride (310 mg), dimethylamine
hydrochloride (270 mg) and triethylamine (0.45 ml), and the
mixture stirred at room temperature for 12 hours. Water
10 and chloroform were added to the reaction mixture, the
organic layer was separated and washed with saturated
aqueous sodium chloride, and dried with magnesium sulfate.
The solvent was distilled off under reduced pressure to
give the titled compound (380 mg).

15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.67-1.71(2H,m), 1.95-2.11(3H,m),
2.37-2.71(8H,m), 2.97(3H,s), 3.08(3H,s), 4.64(2H,s),
5.27(2H,brs), 6.09(1H,t), 6.74-6.82(2H,m), 6.93(1H,d),
7.24-7.44(5H,m), 7.58(1H,dd), 8.47(1H,dd).

MS m/z: 548 (M+1)

20 Example 135 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-morpholinocarbonylmethyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
procedure of example 134, but replacing dimethylamine
25 hydrochloride with morpholine.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.67-1.71(2H,m), 1.87(1H,brs),
2.00-2.11(2H,m), 2.38-2.71(8H,m), 3.61-3.68(8H,m),

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4.65 (2H, s), 5.27 (2H, brs), 6.09 (1H, t), 6.74-6.83 (2H, m),
6.90 (1H, d), 7.25-7.44 (5H, m), 7.58 (1H, dd), 8.48 (1H, dd).
MS m/z: 590 (M+1)

Example 138 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-
5 (1-ethoxycarbonyl-1-methylethyl)oxy[1]benzoxepino[2,3-
b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
procedure of example 46, but replacing ethyl iodide with
ethyl 2-bromoisobutyrate.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.27 (3H, t), 1.56 (6H, s), 1.63-1.71 (3H, m),
2.01-2.10 (2H, m), 2.35-2.70 (8H, m), 4.24 (2H, q), 5.28 (2H, brs),
6.05 (1H, t), 6.67-6.75 (2H, m), 6.87 (1H, d), 7.24-7.44 (5H, m),
7.56 (1H, dd), 8.49 (1H, dd).

MS m/z: 577 (M+1)

15 Example 139 - 1-[3-(7-(1-Carboxy-1-methylethyl)oxy-5,11-
dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-
(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the
procedure of example 133, but replacing product of example
20 48 with product of example 138.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.45-1.52 (8H, m), 1.79-1.85 (2H, m),
2.28-2.53 (8H, m), 5.19 (2H, brs), 6.07 (1H, t), 6.69-6.73 (2H, m),
6.85 (1H, d), 7.33-7.47 (5H, m), 7.71 (1H, dd), 8.48 (1H, dd).
MS m/z: 549 (M+1)

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Example 140 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-methoxyphenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-methoxyphenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.62-1.75 (2H,m), 2.08 (2H,dt), 2.41-2.76 (9H,m), 3.77 (3H,s), 3.78 (3H,s), 5.26 (2H,brs), 6.06 (1H,t), 6.75-6.871 (5H,m), 7.23 (1H,dd), 7.38 (2H,d), 7.57 (1H,dd), 8.45 (1H,dd).
MS m/z: 473 (M+1)

Example 141 - 4-(4-Cyanophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-cyanophenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.58-1.70 (2H,m), 2.03 (2H,t), 2.31-2.64 (7H,m), 2.65-2.78 (2H,m), 3.75 (3H,s), 5.26 (2H,brs), 5.95 (0.1H,t, E isomer), 6.05 (0.9H,t, Z isomer), 6.70-6.80 (3H,m), 7.22 (1H,dd), 7.54-7.68 (5H,m), 8.31 (0.1H,dd, E isomer), 8.39 (0.9H,dd, Z isomer).
MS m/z: 468 (M+1)

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Example 142 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-hydroxyphenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-hydroxyphenyl)-4-hydroxypiperidine.

¹HNMR (CDCl₃) δ: 1.76-1.88 (2H, m), 2.08-2.22 (2H, m), 2.45-2.95 (9H, m), 3.76 (3H, s), 5.28 (2H, brs), 5.95 (0.3H, t, E isomer), 6.04 (0.7H, t, Z isomer), 6.69-6.72 (3H, m), 6.90 (2H, d), 7.20-7.30 (3H, m), 7.56 (0.7H, dd, Z isomer), 7.67 (0.3H, dd, E isomer), 8.46 (0.7H, dd, Z isomer), 8.47 (0.3H, dd, E isomer). OH signal was not observed.

MS m/z: 473 (M+1)

Example 143 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-fluoro-3-methylphenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-fluoro-3-methylphenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.62-1.75 (2H, m), 2.05 (1H, brs), 2.09 (2H, dt), 2.25 (3H, s), 2.30-2.76 (8H, m), 3.76 (3H, s), 5.26 (2H, brs), 5.96 (0.1H, t, E isomer), 6.07 (0.9H, t, Z isomer), 6.75-6.89 (3H, m), 6.93 (1H, t), 7.11-7.20 (0.3H, m, E isomer), 7.21-7.35 (0.24H, m, Z isomer), 7.56 (0.9H, dd, E isomer), 7.67 (0.1H, dd, E isomer), 8.38 (0.1H, dd, E isomer), 8.45 (0.9H, dd, Z isomer).

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MS m/z: 475 (M+1)

Example 144 - 4-(3,4-difluorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

5 The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(3,4-difluorophenyl)-4-hydroxypiperidine.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.58-1.72 (2H, m), 1.96 (2H, dt), 2.33-
2.71 (8H, m), 3.73 (3H, s), 5.23 (2H, brs), 5.94 (0.1H, t, E
isomer), 6.04 (0.9H, t, Z isomer), 8.38-8.36 (0.9H, m, Z
isomer), 6.68-6.79 (3H, m), 6.98-7.38 (4H, m), 7.50-
7.62 (0.9H, m, Z isomer), 7.63-7.68 (0.1H, m, E isomer), 8.29-
8.32 (0.1H, m, E isomer), 8.32-8.44 (0.9H, m, Z isomer). OH
15 signal was not observed.

MS m/z: 479 (M+1)

Example 145 - 4-(4-Chloro-3-trifluoromethylphenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

20 The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chloro-3-trifluoromethylphenyl)-4-hydroxypiperidine.

25 $^1\text{H-NMR}$ (CDCl_3) δ : 1.62-1.74 (2H, m), 2.10 (2H, dt), 2.35-
2.80 (8H, m), 2.42 (1H, brs), 3.76 (3H, s), 5.26 (2H, brs),
6.07 (0.9H, t, Z isomer), 6.03 (0.1H, t, E isomer), 6.82-
6.71 (3H, m), 7.24 (1H, dd), 7.43 (1H, d), 7.56 (1.8H, dd, Z

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isomer), 7.65(0.2H,dd, E isomer) 7.83(1H,d), 8.36(0.1H,dd, E isomer), 8.44(0.9H,dd, Z isomer),
MS m/z: 545(M+1)

Example 146 - 4-(3,5-dichlorophenyl)-1-[3-(5,11-dihydro-
5 methoxy[1]benzoxepino[2,3-b]pyridin-5-
ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
10 4-(3,5-dichlorophenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.58-2.22(5H,m), 2.38-2.77(8H,m),
3.76(3H,s), 5.26(2H,brs), 5.92(0.1H,t, E isomer),
6.07(0.9H,t, Z isomer), 6.83-6.71(3H,m), 7.19-7.42(4H,m),
7.56(0.9H,dd, Z isomer), 7.68(0.1H,dd, E isomer),
15 8.38(0.1H,dd, E isomer), 8.45(0.9H,dd, Z isomer).

MS m/z: 512(M+1)

Example 147 - 1-[3-(5,11-Dihydro-7-
methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-
(2-pyridyl)piperidin-4-ol

20 The titled compound was prepared by following the
procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(2-pyridyl)-4-hydroxypiperidine

¹H-NMR (CDCl₃) δ: 1.54-1.65(2H,m), 2.06(2H,dt),
25 2.07(1H,brs), 2.35-2.62(7H,m), 2.73-2.87(2H,m),
3.78(3H,s), 5.28(2H, brs), 6.08(1H,t), 6.72-6.85(3H,m),
7.14-7.29(2H,m), 7.57(1H,d), 7.70(1H,dd), 8.48(2H,dd).

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MS m/z: 444 (M+1)

Example 148 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(3-pyridyl)piperidin-4-ol

5 The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(3-pyridyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.65-1.78 (2H, m), 2.08 (2H, dt), 2.37-2.88 (7H, m), 2.63-2.79 (2H, m), 3.78 (3H, s), 5.28 (2H, brs), 6.02 (0.1H, t, E isomer), 6.07 (0.9H, t, Z isomer), 6.70-6.84 (3H, m), 7.22-7.32 (3H, m), 7.56 (1H, dd), 7.77 (1H, dd), 8.46 (0.9H, d), 8.57 (0.1H, dd, E isomer), 8.73 (1H, dd).

MS m/z: 444 (M+1)

15 Example 149 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-pyridyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-pyridyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.58-1.72 (2H, m), 2.03 (2H, dt), 2.34-2.89 (8H, m), 2.96 (1H, brs), 3.76 (3H, s), 5.25 (2H, brs), 6.06 (1H, t), 6.72-6.83 (3H, m), 7.24 (1H, dd), 7.37 (2H, dd), 7.56 (1H, dd), 8.45 (1H, dd), 8.48 (2H, dd).

MS m/z: 444 (M+1)

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Example 150 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-trifluoromethylphenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-trifluoromethylphenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.64-1.75 (2H, m), 2.01 (1H, brs), 2.16 (2H, dt), 2.38-2.86 (8H, m), 3.76 (3H, s), 5.26 (2H, brs), 6.04 (1H, t), 6.72-6.84 (3H, m), 7.23 (1H, dd), 7.56 (5H, m), 8.42 (1H, dd).

MS m/z: 511 (M+1)

Example 151 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 44, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)piperidine.

¹H-NMR (CDCl₃) δ: 1.62-1.92 (4H, m), 1.94-2.18 (2H, m), 2.28-2.64 (5H, m), 2.99 (2H, m), 5.25 (2H, brs), 6.00 (1H, t), 6.60-6.82 (3H, m), 7.02-7.36 (5H, m), 7.50 (1H, dd), 8.47 (1H, dd). OH signal was not observed.

MS m/z: 447 (M+1)

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Example 152 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 46, but replacing the product of example 44 with the product of example 151.

¹H-NMR (CDCl₃) δ: 1.40 (3H, t), 1.52-2.14 (6H, m), 2.30-2.57 (5H, m), 2.94 (2H, m), 4.00 (2H, q), 5.28 (2H, brs), 6.07 (1H, t), 6.68-6.86 (3H, m), 7.05-7.36 (5H, m), 7.58 (1H, m), 8.49 (1H, m).

MS m/z: 475 (M+1)

Example 153 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethoxycarbonylmethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 48, but replacing the product of example 44 with the product of example 151.

¹H-NMR (CDCl₃) δ: 1.29 (3H, t), 1.56-1.85 (4H, m), 1.99 (2H, dt), 2.28-2.55 (5H, m), 2.91 (2H, m), 4.27 (2H, q), 4.58 (2H, s), 5.28 (2H, brs), 6.09 (1H, t), 6.68-6.95 (3H, m), 7.07-7.32 (5H, m), 7.58 (1H, dd), 8.49 (1H, dd).

MS m/z: 533 (M+1)

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Example 154 - 1-[3-(7-(Carboxymethoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidine

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 153.

¹H-NMR (CD₃OD) δ: 1.82-2.17 (4H, m), 2.69 (2H, m), 2.86 (1H, m), 3.07 (2H, m), 3.30 (2H, m), 3.57 (2H, m), 4.57 (2H, s), 5.21 (2H, brs), 6.10 (1H, t), 6.70-7.04 (3H, m), 7.16-

7.38 (4H, m), 7.44 (1H, m), 7.77 (1H, m), 8.47 (1H, m). COOH signal was not observed.

MS m/z: 505 (M+1)

Example 155 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-dimethylaminocarbonylmethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 134, but replacing the product of example 133 with the product of example 154.

¹H-NMR (CDCl₃) δ: 1.58-1.92 (4H, m), 2.04 (2H, m), 2.30-2.68 (5H, m), 2.93 (2H, m), 2.98 (3H, s), 3.08 (3H, s), 4.65 (2H, s), 5.28 (2H, brs), 6.07 (1H, t), 6.70-6.98 (3H, m), 7.08-7.36 (5H, m), 7.60 (1H, m), 8.50 (1H, m).

MS m/z: 532 (M+1)

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Example 156 - 1-[3-(7-(2-Acetoxyethyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 50, but replacing the product of example 44 with the product of example 151.

¹H-NMR (CDCl₃) δ: 1.55-1.88 (4H, m), 1.90-2.32 (2H, m), 2.10 (3H, s), 2.28-2.60 (5H, m), 2.82-3.02 (2H, m), 4.14 (2H, dd), 4.41 (2H, dd), 5.29 (2H, brs), 6.08 (1H, t), 6.72-6.90 (3H, m), 7.18-7.34 (5H, m), 7.57 (1H, m), 8.50 (1H, m).
MS m/z: 533 (M+1)

Example 157 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-hydroxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 51, but replacing the product of example 50 with the product of example 156.

¹H-NMR (CD₃OD) δ: 1.66-1.98 (4H, m), 2.40-2.73 (5H, m), 2.82-2.94 (2H, m), 3.22 (2H, m), 3.84 (2H, dd), 4.01 (2H, dd), 5.23 (2H, brs), 6.13 (1H, t), 6.64-6.98 (3H, m), 7.13-7.34 (4H, m), 7.45 (1H, m), 7.77 (1H, m), 8.47 (1H, m). OH signal was not observed.
MS m/z: 491 (M+1)

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Example 158 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-ethoxycarbonyl-1-methylethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 138, but replacing the product of example 44 with the product of example 151.

¹H-NMR (CDCl₃) δ: 1.28(3H,t), 1.56(6H,s), 1.56-1.85(4H,m), 1.97(2H,dt), 2.28-2.55(5H,m), 2.93(2H,m), 4.24(2H,q), 5.28(2H,brs), 6.04(1H,t), 6.62-6.95(3H,m), 7.07-7.32(5H,m), 7.57(1H,dd), 8.50(1H,dd).
MS m/z: 561(M+1)

Example 159 - 1-[3-(7-(1-Carboxy-1-methylethyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidine

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 158.

¹H-NMR (CD₃OD) δ: 1.50(6H,s), 1.82-2.18(4H,m), 2.70(2H,m), 2.87(1H,m), 3.12(2H,m), 3.30(2H,m), 3.60(2H,m), 5.25(2H,brs), 6.07(1H,t), 6.67-7.04(3H,m), 7.16-7.38(4H,m), 7.58(1H,m), 7.96(1H,m), 8.52(1H,m). COOH signal was not observed.
MS m/z: 533(M+1)

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Example 160 - 1-[3-(8-Bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidine

The titled compound was prepared by following the procedure of example 65, but replacing the product of example 45, step 2 with the product of example 54, step 1.

¹H-NMR (CDCl₃) δ: 1.50-1.86(4H,m), 1.98(2H,m), 2.26-2.60(5H,m), 2.88(2H,m), 5.30(2H,brs), 6.09(1H,t), 6.96-7.36(8H,m), 7.57(1H,dd), 8.51(1H,dd).

MS m/z: 509, 511(M+1)

Example 161 - 1-[3-(8-Carboxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidine

To a solution of 1-[3-(8-Bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidine (Example 161) (130 mg) in THF(1.0 ml) was added 1.6M n-butyllithium hexane solution (0.17 ml) at -78°C. After stirring 10 minutes at the same temperature, CO₂ (dry-ice) was added to the mixture. After being warmed to ambient temperature, the mixture was stirred for 30 minutes at the same temperature. The mixture was concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography eluted with dichloromethane -methanol (5:1) to give the titled compound

¹H-NMR (CD₃OD) δ: 1.55-1.95(4H,m), 2.17(2H,dt), 2.32-2.78(5H,m), 3.00(2H,m), 5.30(2H,brs), 6.19(1H,t), 7.08-

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7.54(8H,m), 7.76(1H,dd), 8.45(1H,dd). COOH signal was not observed (50 mg).

MS m/z: 475(M+1)

Example 162 - 1-[3-(7-Bromo-5,11-

5 dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, but replacing

5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one

10 with

8-bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-one.

1H-NMR (CDCl₃) δ: 1.60-1.71(3H,m), 1.98-2.09(2H,m), 2.34-2.69(8H,m), 5.32(2H,brs), 6.13(1H,t), 6.73(1H,d), 7.22-7.44(7H,m), 7.57(1H,dd), 8.52(1H,dd).

15 MS m/z: 525, 527(M+1)

Example 163 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, but replacing

5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with

5,11-dihydro-7-ethyl[1]benzoxepino[2,3-b]pyridin-5-one.

1H-NMR (CDCl₃) δ: 1.23(3H,t), 1.52(1H,brs),

25 1.66-1.71(2H,m), 1.98-2.06(2H,m), 2.35-2.70(11H,m),

5.31(2H,brs), 6.09(1H,t), 6.79(1H,d), 7.01(1H,dd),

7.11(1H,d), 7.25-7.44(5H,m), 7.58(1H,dd), 8.49(1H,dd).

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MS m/z: 475 (M+1)

Example 164 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-8-vinyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

5 The titled compound was prepared by following the procedure of example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11-dihydro-8-vinyl[1]benzoxepino[2,3-b]pyridin-5-one.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.66-1.71 (3H, m), 2.00-2.10 (2H, m), 2.36-2.70 (8H, m), 5.22 (2H, d), 5.34 (2H, brs), 5.70 (1H, d), 6.11 (1H, t), 6.61 (1H, dd), 6.89 (1H, d), 6.99 (1H, dd), 7.24-7.44 (6H, m), 7.58 (1H, dd), 8.49 (1H, dd).

MS m/z: 473 (M+1)

15 Example 165 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-8-ethyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

A mixture of the product of example 164 (100 mg) and Pd-C (20 mg) in ethanol (2 ml) stirred under a hydrogen balloon at room temperature for 1 hour. The mixture was filtered through the celite and distilled off under reduced pressure. The residue was purified by preparative thin layer chromatography eluting with chloroform-methanol (15:1) to give the titled compound (50 mg).

25 $^1\text{H-NMR}$ (CDCl_3) δ : 1.22 (3H, t), 1.55-1.77 (3H, m), 2.00-2.13 (2H, m), 2.33-2.74 (10H, m), 5.32 (2H, brs),

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6.07(1H,t), 6.70(1H,d), 6.78(1H,dd), 7.19-7.44(6H,m),
7.57(1H,dd), 8.49(1H,dd).

MS m/z: 475 (M+1)

Example 166 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-9-

5 methoxy[1]benzoxepino[2,3-b]pyridin-5-
ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
procedure of example 45, but replacing

5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one

10 with

5,11-dihydro-9-methoxy[1]benzoxepino[2,3-b]pyridin-5-one.

1H-NMR (CDCl₃) δ: 1.65-1.70(2H,m), 1.95-2.06(2H,m),
2.15(1H,brs), 2.37-2.67(8H,m), 3.83(3H,s), 5.43(2H,brs),
6.09(1H,t), 6.79-6.91(3H,m), 7.22-7.43(5H,m), 7.57(1H,dd),
8.44(1H,dd).

MS m/z: 477 (M+1)

Example 167 - 4-(4-Chlorophenyl)-1-[3-(5,11-
dihydro[1]benzoxepino[4,3-c]pyridin-5-
ylidene)propyl]piperidin-4-ol

20 The titled compound was prepared by following the
procedure of example 45, but replacing

5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one
with 5,11- dihydro[1]benzoxepino[4,3-c]pyridin-5-one.

1H-NMR (CDCl₃) δ: 1.67-1.71(2H,m), 1.97-2.08(2H,m),

25 2.16(1H,s), 2.40-2.69(8H,m), 5.16(2H,brs), 6.14(1H,t),
6.80(1H,dd), 6.91-6.97(1H,m), 7.13-7.19(1H,m),
7.26-7.44(6H,m), 7.50-8.54(2H,m).

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MS m/z: 447 (M+1)

Example 168 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro[1]benzoxepino[4,3-d]pyrimidin-5-ylidene)propyl]piperidin-4-ol

5 The titled compound was prepared by following the procedure of example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11-dihydro[1]benzoxepino[4,3-d]pyrimidin-5-one.
1H-NMR (CDCl₃) δ: 1.68-1.72 (2H, m), 1.90 (1H, brs),
10 2.06-2.19 (2H, m), 2.41-2.78 (8H, m), 5.20 (2H, s), 6.12 (1H, t),
- 7.14-7.45 (8H, m), 8.72 (1H, s), 8.97 (1H, s).

MS m/z: 448 (M+1)

Example 169 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-trifluoromethanesulfonyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

15 To a solution of product of example 44 (1.0 g) in pyridine (10 ml) was added trifluoromethanesulfonic acid anhydride (0.55 ml) at 0°C, and the mixture was stirred at room temperature for 1 hour. Water and diethyl ether were
20 added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography eluting with
25 ethyl acetate-methanol (10:1) to give the titled compound (1.1 g).

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1H-NMR (CDCl₃) δ: 1.56 (1H, brs), 1.66-1.71 (2H, m),
1.97-2.09 (2H, m), 2.35-2.69 (8H, m), 5.35 (2H, brs) 6.15 (1H, t),
6.88 (1H, d), 7.05 (1H, dd), 7.21-7.44 (6H, m), 7.60 (1H, dd),
8.54 (1H, dd).

5 MS m/z: 595 (M+1)

Example 170 - 1-[3-(7-Allyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

To a mixture of the product of example 169 (240 mg),

10 allyltributyltin (0.19 ml),
dichlorobis(triphenylphosphine)palladium(II) (30 mg),
lithium chloride (76 mg), in dimethylformamide (3 ml)
under argon at 120°C for 2 hours. Aqueous ammonium fluoride
solution and ethyl acetate were added to the reaction
15 mixture, the organic layer was separated and washed with
saturated aqueous sodium chloride, and dried with
magnesium sulfate. The solvent was distilled off under
reduced pressure, and the residue was purified by silica
gel chromatography eluting with chloroform-methanol (10:1)
20 to give the titled compound (180 mg).

1H-NMR (CDCl₃) δ: 1.62-1.72 (3H, m), 2.03-2.11 (2H, m),
2.39-2.73 (8H, m), 3.31 (2H, d), 5.04-5.11 (2H, m),
5.29 (2H, brs), 5.87-6.02 (1H, m), 6.06 (1H, t), 6.77 (1H, d),
6.99 (1H, dd), 7.10 (1H, d), 7.23-7.43 (5H, m), 7.57 (1H, dd),
25 8.40 (1H, dd).

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Example 171 - 1-[3-(7-(2-t-Butoxycarboxy)ethenyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

A mixture of the product of example 169 (1.7 g),
5 t-butyl acrylate (0.85 ml), triethylamine (2.5 ml),
1,1'-bis(diphenylphosphino)ferrocene (250 mg) and
palladium(II) diacetate (33 mg) in dimethylformamide (3
ml) under argon at 90°C for 24 hours. Water ethyl acetate
were added to the reaction mixture, the organic layer was
10 separated and washed with saturated aqueous sodium
chloride, and dried with magnesium sulfate. The solvent
was distilled off under reduced pressure, and the residue
was purified by silica gel chromatography eluting with
ethyl acetate-methanol (30:1) to give the titled compound
15 (780 mg).

1H-NMR (CDCl₃) δ: 1.45 (9H, s), 1.63-1.71 (3H, m),
1.98-2.10 (2H, m), 2.35-2.72 (8H, m), 5.35 (2H, brs),
6.15 (1H, t), 6.26 (1H, d), 6.83 (1H, d), 7.22-7.44 (7H, m),
7.53 (1H, d), 7.58 (1H, dd), 8.52 (1H, dd).

20 Example 172 - 1-[3-(7-(2-Carboxy)ethenyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The product of example 171 (330 mg) was dissolved
with 4N hydrochloric acid 1,4-dioxane solution (4 ml), and
25 stirred at room temperature for 1 hour. The solvent was
distilled off under reduced pressure. Water was added to
the residue, and neutralized with sodium hydroxide

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solution. The precipitation was filtered to give the titled compound (190 mg).

1H-NMR (DMSO-d₆) δ: 1.45-1.52 (2H, m), 1.72-1.84 (2H, m), 2.25-2.58 (8H, m), 5.25 (2H, brs), 6.28 (1H, t), 6.43 (1H, d), 5 6.82 (1H, d), 7.34-7.60 (8H, m), 7.75 (1H, dd), 8.52 (1H, dd).

Example 173 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-propargyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the 10 procedure of example 46, but replacing ethyl iodide with propargyl chloride.

1H-NMR (CDCl₃) δ: 1.66-1.71 (2H, m), 1.79 (1H, brs), 1.99-2.10 (2H, m), 2.35-2.71 (9H, m), 4.66 (2H, d), 5.28 (2H, brs), 6.10 (1H, t), 6.80-6.93 (3H, m), 15 7.24-7.46 (5H, m), 7.59 (1H, dd), 8.48 (1H, dd).
MS m/z: 501 (M+1)

Example 174 - 4-(4-Chlorophenyl)-1-[3-(7-cyclopentoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

20 The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with cyclopentyl bromide.

1H-NMR (CDCl₃) δ: 1.54-2.18 (13H, m), 2.41-2.72 (8H, m), 4.66-4.73 (1H, m), 5.27 (2H, brs), 6.08 (1H, t), 25 6.70-6.87 (3H, m), 7.23-7.44 (5H, m), 7.58 (1H, dd), 8.49 (1H, dd).
MS m/z: 531 (M+1)

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Example 175 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-methoxyethyl)oxy)[1]benzoxepino[2,3-b]pyridin-5-ylidene]propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with 2-methoxyethyl chloride.

1H-NMR (CDCl₃) δ: 1.66-1.75 (3H, m), 2.00-2.11 (2H, m),
2.36-2.71 (8H, m), 3.45 (3H, s), 3.71-3.75 (2H, m),
4.07-4.11 (2H, m), 5.27 (2H, brs), 6.09 (1H, t),
10 6.75-6.91 (3H, m), 7.23-7.44 (5H, m), 7.57 (1H, dd),
8.48 (1H, dd).

MS m/z: 521 (M+1)

Example 176 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-dimethyaminocarbonyl-1-methylethyl)oxy)[1]benzoxepino[2,3-b]pyridin-5-ylidene]propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 134, but replacing the product of example 133 with the product of example 139.

1H-NMR (CDCl₃) δ: 1.59 (6H, s), 1.67-1.72 (2H, m),
1.99-2.09 (2H, m), 2.36-2.70 (9H, m), 2.96 (3H, s), 3.21 (3H, s),
5.25 (2H, brs), 6.02 (1H, t), 6.60-6.77 (3H, m),
7.24-7.44 (5H, m), 7.58 (1H, dd), 8.44 (1H, dd).

MS m/z: 576 (M+1)

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Example 177 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-ethoxycarbonylethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with ethyl 2-bromopropionate.

1H-NMR (CDCl₃) δ: 1.25 (3H, t), 1.59 (3H, d), 1.65-1.70 (2H, m), 1.98-2.08 (2H, m), 2.35-2.68 (8H, m), 2.80 (1H, brs), 4.21 (2H, q), 4.68 (1H, q), 5.24 (2H, brs), 6.07 (1H, t), 10 6.68-6.79 (2H, m), 6.88 (1H, d), 7.22-7.44 (5H, m), 7.56 (1H, dd), 8.40 (1H, dd).

Example 178 - 1-[3-(7-(1-Carboxyethyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

15 The titled compound was prepared by following the procedure of example 133, but replacing product of example 48 with product of example 177.

1H-NMR (DMSO-d₆) δ: 1.46 (3H, d), 1.58-1.63 (2H, m), 1.98-2.06 (2H, m), 2.41-2.45 (2H, m), 2.72-2.86 (6H, m), 20 4.74 (1H, q), 5.18 (2H, brs), 6.11 (1H, t), 6.73 (2H, s), 6.84 (1H, s), 7.36-7.47 (5H, m), 7.73 (1H, dd), 8.50 (1H, dd).

MS m/z: 535 (M+1)

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1H-NMR (CDCl₃) δ: 1.66-1.71 (2H, m), 1.98-2.09 (2H, m),
2.21 (1H, brs), 2.38-2.70 (8H, m), 4.45 (2H, s), 5.28 (2H, brs),
6.09 (1H, t), 6.11 (1H, brs), 6.58 (1H, brs), 6.74-6.85 (3H, m),
7.24-7.44 (5H, m), 7.58 (1H, dd), 8.47 (1H, dd).

5 MS m/z: 520 (M+1)

Example 182 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methylaminocarbonylmethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
10 procedure of example 134, but replacing dimethylamine
hydrochloride with methylamine.

1H-NMR (CDCl₃) δ: 1.67-1.72 (2H, m), 1.99-2.10 (2H, m),
2.36-2.70 (9H, m), 2.89 (3H, d), 4.45 (2H, s), 5.28 (2H, brs),
6.08 (1H, t), 6.66 (1H, brs), 6.73-6.84 (3H, m),
15 7.25-7.45 (5H, m), 7.58 (1H, dd), 8.47 (1H, dd).
MS m/z: 534 (M+1)

Example 183 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-[3-c] [1]benzoxepinepin-5-ylidene)propyl]-4-(4-hydroxyphenyl)piperidine

The titled compound was prepared by following the
procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(4-hydroxyphenyl)piperidine.

25 1H-NMR (CDCl₃) δ: 1.52-1.88 (4H, m), 2.01 (2H, dt), 2.28-
2.60 (5H, m), 2.93 (2H, m), 3.79 (3H, s), 5.28 (2H, brs),

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Example 179 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-ethoxycarbonyl)cyclbutoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
5 procedure of example 46, but replacing ethyl iodide with
ethyl 2-bromocyclbutanecarboxylate.

1H-NMR (CDCl₃) δ: 1.19(3H,t), 1.67-1.71(2H,m),
1.92-2.11(5H,m), 2.33-2.77(12H,m), 4.21(2H,q),
5.25(2H,brs), 6.05(1H,t), 6.47(1H,dd), 6.70(1H,d),
10 6.73(1H,d), 7.23-7.44(5H,m), 7.55(1H,dd), 8.44(1H,dd).

Example 180 - 1-[3-(7-(1-Carboxy)cyclbutoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the
15 procedure of example 133, but replacing product of example
48 with product of example 179.

1H-NMR (DMSO-d₆) δ: 1.60-1.65(2H,m), 1.86-2.08(4H,m),
2.24-2.90(12H,m), 5.17(2H,brs), 6.05(1H,t), 6.50(1H,dd),
6.66(1H,d), 6.73(1H,d), 7.37-7.48(5H,m), 7.74(1H,dd),
20 8.51(1H,dd).

MS m/z: 561(M+1)

Example 181 - 1-[3-(7-Carbamoylmethyloxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

25 The titled compound was prepared by following the
procedure of example 134, but replacing dimethylamine
hydrochloride with ammonium hydroxide.

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6.08 (1H, t), 6.68-6.88 (3H, m), 7.05-7.36 (5H, m), 7.58 (1H, dd),
8.50 (1H, dd).

MS m/z: 461 (M+1)

Example 184 - 1-[3-(5,11-Dihydro-7-

5 methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-[3-c][1]benzoxepiepin-5-ylidene)propyl]-4-(2-hydroxyphenyl)piperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing
10 4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(2-hydroxyphenyl)piperidine.

¹H-NMR (CDCl₃) δ: 1.78-1.92 (4H, m), 2.12-2.25 (2H, m), 2.32-
2.70 (4H, m), 2.80-2.97 (1H, m), 3.01-3.15 (2H, m), 3.77 (3H, s),
3.78 (1H, brs), 5.28 (2H, brs), 6.03 (1H, t), 6.74-6.86 (4H, m),
15 7.05 (1H, dd), 7.11 (1H, dd), 7.23-7.28 (2H, m), 7.56 (1H, dd),
8.48 (1H, dd), OH signal was not observed.

MS m/z: 443 (M+1)

Example 185 - 4-(7-Chloro-1,2-benzisoxazol-3-yl)-1-[3-

(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-

20 ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(7-chloro-1,2-benzisoxazol-3-yl) piperidine. This
25 piperidine was prepared by the same method described in *J.
Med. Chem.* 28:761-769 (1985).

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¹H-NMR (CDCl₃) δ: 1.94-2.20 (6H, m), 2.30-2.60 (4H, m), 2.86-3.14 (3H, m), 3.79 (3H, s), 5.29 (2H, brs), 6.10 (1H, t), 6.70-6.88 (3H, m), 7.22 (1H, t), 7.27 (1H, dd), 7.50 (1H, dd), 7.57-7.68 (2H, m), 8.49 (1H, dd).

5 Example 186 - 4-(7-Chloroindol-3-yl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing
10 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(7-chloroindol-3-yl)piperidine. This piperidine was prepared by the same method described in *J. Med. Chem.* 36:4006-4014 (1993) and following hydrogenation described in Example 58, step 3.

15 ¹H-NMR (CDCl₃) δ: 1.66-1.88 (2H, m), 1.92-2.22 (4H, m), 2.32-2.63 (4H, m), 2.78 (1H, m), 2.97 (2H, m), 3.79 (3H, s), 5.29 (2H, brs), 6.09 (1H, t), 6.70-6.87 (3H, m), 6.97-7.07 (2H, m), 7.12-7.30 (2H, m), 7.52 (1H, m), 7.59 (1H, dd), 8.45 (1H, brs), 8.50 (1H, dd).

20 Example 187 - 4-Azido-4-(4-chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing
25 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-azido-4-(4-chlorophenyl) piperidine.

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¹H-NMR (CDCl₃) δ: 1.88 (2H, m), 2.55-2.85 (4H, m), 3.00-3.30 (6H, m), 3.75 (3H, s), 5.19 (2H, brs), 5.97 (1H, t), 6.68-6.65 (3H, m), 7.20-7.46 (5H, m), 7.63 (1H, dd), 8.35 (1H, dd).
MS m/z: 477 (M+1-N₂+H₂)

5 Example 188 - Methyl 1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-phenylpiperidin-4-carboxylate

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 10 4-(4-chlorophenyl)-4-hydroxypiperidine with methyl 4-phenylpiperidin-4-carboxylate.

¹H-NMR (CDCl₃) δ: 1.82-2.15 (4H, m), 2.28-2.60 (6H, m), 2.78-2.82 (2H, m), 3.62 (3H, s), 3.68 (3H, s), 5.26 (2H, brs), 5.95 (0.1H, t, E isomer), 6.05 (0.9H, t, Z isomer), 6.82-15 6.70 (3H, m), 7.33-7.22 (6H, m), 7.65 (0.1H, dd, Z isomer), 7.55 (0.9H, dd, Z isomer), 8.39 (0.1H, E isomer), 8.48 (0.9H, dd, Z isomer).

MS m/z: 485 (M+1)

Example 189 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-phenylpiperidin-4-carboxylic acid

The titled compound was prepared by following the procedure of example 133, but replacing product of example 48 with product of example 188.

25 ¹H-NMR (CD₃OD) δ: 2.16-2.23 (2H, m), 2.69-2.91 (4H, m), 3.00-3.16 (2H, m), 3.37-3.25 (2H, m), 3.68-3.73 (2H, m), 3.76 (3H, s), 5.34 (2H, brs), 6.24 (1H, t), 6.70-7.04 (3H, m), 7.26-

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7.55 (5H, m), 7.79-7.89 (1H, m), 8.21-8.34 (1H, m), 8.56-
8.62 (0.1H, m), 8.63-8.77 (0.9H, m),
MS m/z: 471 (M+1)

Example 190 - 1-(2-Chlorophenylsulfonyl)-4-[3-(5,11-
5 Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-
ylidene)propyl]piperazine

The titled compound was prepared by following the
procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
10 1-(2-chlorophenylsulfonyl)piperazine.

¹H-NMR (CDCl₃) δ: 2.20-2.58 (8H, m), 3.12-3.38 (4H, m),
3.76 (3H, s), 5.22 (2H, brs), 6.03 (1H, t), 6.64-6.90 (3H, m),
7.23 (1H, dd), 7.32-7.60 (4H, m), 8.01 (1H, dd), 8.48 (1H, dd).
MS m/z: 526 (M+1)

15 Example 191 - 1-(3-Chlorophenylsulfonyl)-4-[3-(5,11-
Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-
ylidene)propyl]piperazine

The titled compound was prepared by following the
procedure of example 45, step 3, but replacing
20 4-(4-chlorophenyl)-4-hydroxypiperidine with
1-(3-chlorophenylsulfonyl)piperazine.

¹H-NMR (CDCl₃) δ: 2.20-2.60 (8H, m), 2.82-3.12 (4H, m),
3.76 (3H, s), 5.18 (2H, brs), 6.00 (1H, t), 6.64-6.90 (3H, m),
7.23 (1H, dd), 7.42-7.78 (5H, m), 8.48 (1H, dd).
25 MS m/z: 526 (M+1)

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Example 192 - 1-(4-Chlorophenylsulfonyl)-4-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperazine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-(4-chlorophenylsulfonyl)piperazine.

¹H-NMR (CDCl₃) δ: 2.20-2.56 (8H, m), 2.82-3.10 (4H, m), 3.76 (3H, s), 5.18 (2H, brs), 5.99 (1H, t), 6.62-6.92 (3H, m), 7.23 (1H, dd), 7.42-7.78 (5H, m), 8.48 (1H, dd).

MS m/z: 526 (M+1)

Example 193 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-1,2,3,6-tetrahydropyridine

The titled compound was prepared by following the procedure of example 44, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine.

¹H-NMR (CDCl₃) δ: 2.37-2.72 (8H, m), 3.07 (2H, m), 5.25 (2H, brs), 6.00 (1H, m), 6.07 (1H, t), 6.60-6.78 (3H, m), 7.18-7.47 (5H, m), 7.56 (1H, dd), 8.50 (1H, dd). OH signal was not observed.

MS m/z: 445 (M+1)

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Example 194 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-1,2,3,6-tetrahydropyridine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine.

¹H-NMR (CDCl₃) δ: 2.37-2.72(8H,m), 3.06(2H,m), 3.78(3H,s), 5.27(2H,brs), 5.99(1H,m), 6.10(1H,t), 6.72-6.90(3H,m),

7.20-7.44(5H,m), 7.60(1H,dd), 8.50(1H,dd).

MS m/z: 459 (M+1)

Example 195 - 4-(7-Chloroindol-3-yl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-1,2,3,6-tetrahydropyridine.

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(7-chloroindol-3-yl)-1,2,3,6-tetrahydropyridine. This piperidine was prepared by the same method described in *J. Med. Chem.* 36:4006-4014 (1993).

¹H-NMR (CDCl₃) δ: 2.37-2.76(8H,m), 3.14(2H,m), 3.78(3H,s), 5.29(2H,brs), 6.02-6.23(2H,m), 6.67-6.90(3H,m), 7.05(1H,dd), 7.12-7.33(3H,m), 7.60(1H,dd), 7.77(1H,m), 8.50(1H,dd), 9.06(1H,br s).

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Example 196 - 5-Chloro-1'-(3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)spiro[isobenzofuran-1(3H),4'-piperidine]

The titled compound was prepared by following the
5 procedure of example 44, step 2, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
5-chlorospiro[isobenzofuran-1(3H),4'-piperidine].
1H-NMR (CDCl₃) δ: 1.66-1.71 (2H, m), 1.79-1.91 (2H, m),
2.26-2.73 (8H, m), 4.99 (2H, s), 5.22 (2H, brs), 6.07 (1H, t),
10 6.63-6.70 (2H, m), 6.76 (1H, d), 7.06 (1H, d), 7.19-7.32 (3H, m),
7.60 (1H, dd), 8.47 (1H, dd), 8.63 (1H, s).
MS m/z: 475 (M+1)

Example 197 - 5-Chloro-1'-(3-(5,11-dihydro-7-(2-methoxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)spiro[isobenzofuran-1(3H),4'-piperidine]

The titled compound was prepared by following the
procedure of example 175, but replacing the product of
example 44 with the product of example 196.

1H-NMR (CDCl₃) δ: 1.69-1.74 (2H, m), 1.83-1.94 (2H, m),
20 2.31-2.76 (8H, m), 3.45 (3H, s), 3.72-3.75 (2H, m),
4.08-4.11 (2H, m), 5.00 (2H, s), 5.28 (2H, brs), 6.09 (1H, t),
6.74-6.82 (2H, m), 6.89 (1H, d), 7.04 (1H, d), 7.17-7.28 (3H, m),
7.57 (1H, dd), 8.49 (1H, dd).
MS m/z: (M+1)

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Example 198 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-dimethylaminocarbonyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 134, but replacing the product of example 133 with the product of example 118.

1H-NMR (CDCl₃) δ: 1.65-1.70 (2H,m), 1.99-2.09 (3H,m), 2.32-2.69 (8H,m), 2.17 (3H,s), 5.35 (2H,brs), 6.15 (1H,t), 6.82 (1H,d), 7.19 (1H,dd), 7.28-7.46 (6H,m), 7.58 (1H,dd), 8.49 (1H,dd).

Example 199 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1,1-dimethyl-2-hydroxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of product of example 138 (500 mg) in methanol (5 ml) was added sodium borohydride (330 mg), and the mixture was heated to reflux for 1 hour. The mixture was distilled off under reduced pressure. Water and ethyl acetate were added to the residue, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography eluting with chloroform-methanol (10:1) to give the titled compound (440 mg).

1H-NMR (CDCl₃) δ: 1.26 (6H,s), 1.66-1.70 (2H,m), 1.79 (1H,brs), 2.00-2.08 (2H,m), 2.37-2.70 (9H,m), 3.58 (2H,s), 5.30 (2H,brs), 6.05 (1H,t), 6.75-6.84 (2H,m), 6.91 (1H,d), 7.26-7.44 (5H,m), 7.58 (1H,dd), 8.49 (1H,dd).

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MS m/z: 535 (M+1)

Example 200 -4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2,2-dimethyl-2-hydroxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

5 To a solution of product of example 48 (500 mg) in tetrahydrofuran (5 ml) was added 0.95M methylmagnesium bromide tetrahydrofuran solution (3.8 ml) at 0°C, and the mixture was stirred at room temperature for 20 minutes. Aqueous ammonium chloride solution and ethyl acetate were
10 added to the mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography eluting with chloroform-methanol
15 (10:1) to give the titled compound (360 mg).

1H-NMR (CDCl₃) δ: 1.34 (6H, s), 1.58 (1H, brs),
1.66-1.71 (2H, m), 1.99-2.10 (2H, m), 2.25 (1H, brs),
2.36-2.71 (8H, m), 3.77 (2H, s), 5.28 (2H, brs), 6.09 (1H, t),
6.74-6.86 (3H, m), 7.24-7.44 (5H, m), 7.57 (1H, dd),
20 8.49 (1H, dd).

MS m/z: 535 (M+1)

Example 234 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidine)propyl]-4-(indol-3-yl)-piperidine

25 The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with

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4-(indol-3-yl)-piperidine. This piperidine was prepared by the same method described in *J. Med. Chem.* 36:4006-4014 (1993) and follow hydrogenation described in Example 58, step 3.

5 ¹H-NMR (CDCl₃) δ: 1.65-1.93 (2H, m), 1.94-2.28 (4H, m), 2.34-
2.70 (4H, m), 2.81 (1H, m), 2.96 (2H, m), 3.78 (3H, s),
5.28 (2H, brs), 6.09 (1H, t), 6.70-7.42 (8H, m), 7.53-
7.72 (2H, m), 8.28 (1H, brs), 8.49 (1H, m).

Example 235 - 1-[3-(5,11-Dihydro-7-

10 methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidine)propyl]-4-(indol-3-yl)-1,2,3,6-tetrahydropyridine.

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with

15 4-(indol-3-yl)-1,2,3,6-tetrahydropyridine. This piperidine was prepared by the same method described in *J. Med. Chem.* 36:4006-4014 (1993).

1H-NMR (CDCl₃) δ: 2.35-2.77 (8H, m), 3.06-3.26 (2H, m),
3.78 (3H, s), 5.29 (2H, brs), 6.05-6.22 (2H, m), 6.70-
6.88 (3H, m), 7.07-7.38 (5H, m), 7.60 (1H, dd), 7.87 (1H, m),
8.42 (1H, brs), 8.50 (1H, m).

Example 236 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(3-(ethoxycarbonyl)propyloxy[1]benzoxipino[2,3-b]pyridin-5-ylidine)propyl)piperidine

25 The titled compound was prepared by following the procedure of example 153, but replacing ethyl bromoacetate with ethyl 4-bromobutyrate.

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¹H-NMR (CDCl₃) δ: 1.26 (3H, t), 1.56-1.85 (4H, m), 2.01 (2H, dt), 2.09 (2H, quint), 2.30-2.60 (7H, m), 2.93 (2H, m), 3.98 (2H, t), 4.15 (2H, q), 5.28 (2H, brs), 6.07 (1H, t), 6.68-6.86 (3H, m), 7.07-7.33 (5H, m), 7.58 (1H, dd), 8.50 (1H, dd).

5 MS m/z: 561 (M+1)

Example 237 - 1-[3-(7-(3-Carboxypropyl)oxy-5,11-dihydro-[1]benzoxepino[2,3-b]pyridin-5-ylidine)propyl]-4-(4-chlorophenyl)-piperidine

10 The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 236.

¹H-NMR (CD₃OD) δ: 1.92-2.20 (6H, m), 2.48 (2H, t), 2.70-3.02 (3H, m), 3.06-3.45 (4H, m), 3.66 (2H, m), 4.01 (2H, t), 15 5.48 (2H, brs), 6.36 (1H, t), 6.85 (2H, s), 7.00 (1H, s), 7.20-7.40 (4H, m), 8.11 (1H, dd), 8.64 (1H, d), 8.81 (1H, d). COOH signal was not observed.

MS m/z: 533 (M+1)

Example 248 - 1'-(3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidine)propyl)-6-methylspiro[4H-3,1-benzoxazine-4,4'-piperidine]-2(1H)-one

20 The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 6-methylspiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

¹H-NMR (CDCl₃) δ: 1.99-2.06 (2H, m), 2.29 (3H, s), 2.32-2.69 (10H, m), 3.77 (3H, s), 5.27 (2H, brs), 6.08 (1H, t), 6.69-

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6.83 (4H, m), 6.94 (1H, s), 7.02 (1H, d), 7.25 (1H, dd),
7.55 (1H, dd), 8.48 (1H, dd), 8.56 (1H, s).

MS m/z: 498 (M+1)

Examples 4-7, 9-11, 13-16, 20, 80-82, 84, 87-88, 92-
5 110, 112-113, 116, 119-127, 129, 136-137, 189, 193-195,
201-233, 236, 238-247 shown in Figure 6 can be prepared by
the schemes set forth in Figures 1 - 5 and 7 and by the
procedures described above.

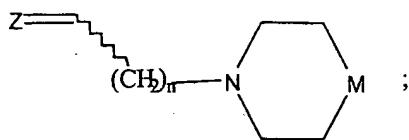
Those skilled in the art will be able to recognize, or
10 be able to ascertain, using no more than routine
experimentation, many equivalents to the specific
embodiments of the invention described herein. Such
equivalents are intended to be encompassed by the
following claims.

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CLAIMS

What is claimed:

1. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation comprising administering to a subject in need thereof an effective amount of a compound represented by the following structural formula:



and physiologically acceptable salts thereof,
10 wherein:

Z is a cycloalkyl or non-aromatic heterocyclic ring group fused to one or more aromatic rings, wherein each ring in Z is independently substituted or unsubstituted;

15 n is an integer from one to about four;

M is >NR² or >CR¹R²;

20 R¹ is -H, -OH, -N₃, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -CN, -COOH, -CO-NR³R⁴ or -NR³R⁴; or

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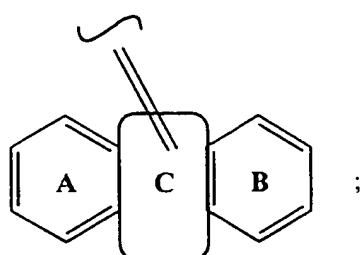
R¹ is a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M

R² is -H, -OH, an acyl group, a substituted acyl group, -NR⁵R⁶, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

R³, R⁴, R⁵ and R⁶ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R¹ and R², R³ and R⁴, or R⁵ and R⁶ taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

20 2. The method of Claim 1 wherein Z is represented by the following structural formula:



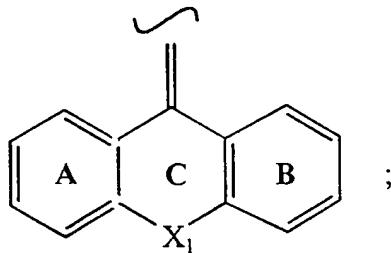
-127-

wherein:

Ring C is a substituted or unsubstituted C₆, C₇ or C₈ non-aromatic carbocyclic ring or a substituted or unsubstituted non-aromatic heterocyclic ring; and

5 Ring A and Ring B are independently substituted or unsubstituted.

3. The method of Claim 2 wherein Z is represented by the structural formula:



wherein:

10 X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-, -O-CH₂-, -CH₂-O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂-, -CH₂-SO-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO- or -CO-NR_c-, wherein:

15 R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted

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aromatic group, a benzyl group or a substituted benzyl group.

4. The method of Claim 3 wherein:

Ring A or Ring B is substituted with -OH,
5 halogen, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group),
-O-(substituted aromatic group), an electron withdrawing group, -(O)_u-(CH₂)_t-C(O)OR²⁰,
- (O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²¹R²² or
10 - (O)_u-(CH₂)_t-NHC(O)O-R²⁰;
R²⁰, R²¹ and R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or
15 R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;
u is zero or one; and
t is an integer from 0 to about 3.

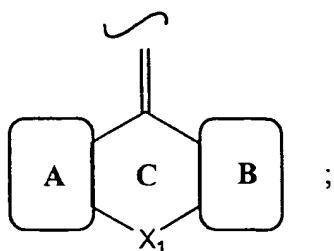
20 5. The method of Claim 3 wherein:

R_c is -(CH₂)_s-COOR³⁰, -(CH₂)_s-C(O)-NR³¹R³² or
- (CH₂)_s-NHC(O)-O-R³⁰;
s is an integer from 1 to about 3; and
25 R³⁰, R³¹ and R³² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

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R^{31} and R^{32} , taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

6. The method of Claim 3 wherein R^1 is -H or -OH.
- 5 7. The method of Claim 3 wherein:
 M is $>C(OH)R^2$; and
 n is two.
8. The method of Claim 7 wherein R^2 is an aromatic or
10 substituted aromatic group.
9. The method of Claim 7 wherein R^2 is an aromatic group substituted with halogen.
10. The method of Claim 9 wherein R^2 is a 4-chlorophenyl group.
- 15 11. The method of Claim 1 wherein Z is represented by the following structural formula:



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wherein:

Ring A is a substituted or unsubstituted heteroaryl group;

5 Ring B is a substituted or unsubstituted aromatic carbocyclic or heteroaryl group;

X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-,
-O-CH₂-, -CH₂-O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂-,
-CH₂-SO-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO- or
-CO-NR_c-; wherein:

10 R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group.

12. The method of Claim 11 wherein:

15 Ring A or Ring B is substituted with -OH, halogen, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group),
-O-(substituted aromatic group), an electron withdrawing group, -(O)_u-(CH₂)_t-C(O)OR²⁰,
- (O)_u-(CH₂)_t-OC(O)R²⁰, - (O)_u-(CH₂)_t-C(O)-NR²¹R²² or
20 - (O)_u-(CH₂)_t-NHC(O)O-R²⁰; wherein:

25 R²⁰, R²¹ or R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

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R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

u is zero or one; and

5 t is an integer from zero to about three.

11. The method of Claim 11, wherein:

X₁ is -NR_c-CH₂-, -CH₂-NR_c-, -NR_c-CO-, or -CO-NR_c-;

R_c is -(CH₂)_s-COOR³⁰, -(CH₂)_s-C(O)-NR³¹R³² or -(CH₂)_s-NHC(O)-O-R³⁰;

10 s is an integer from 1 to about 3;

R³⁰, R³¹ and R³² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

15 R³¹ and R³², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

14. The method of Claim 11 wherein Ring B is a substituted or unsubstituted heteroaryl group.

20 15. The method of Claim 11 wherein Ring A is a substituted or unsubstituted pyridyl group and Ring B is a substituted or unsubstituted aromatic carbocyclic group.

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16. The method of Claim 11 wherein Ring A is a substituted or unsubstituted pyridyl group and Ring B is a substituted or unsubstituted heteroaryl group.

17. The method of Claim 11 wherein R¹ is -H or -OH.

5 18. The method of Claim 11 wherein:

M is >C(OH)R²; and

n is two.

19. The method of Claim 18 wherein R² is an aromatic or substituted aromatic group.

10 20. The method of Claim 18 wherein R² is an aromatic group substituted with halogen.

21. The method of Claim 20 wherein R² is a 4-chlorophenyl group.

22. The method of Claim 11 wherein Ring A is a substituted or unsubstituted heteroaryl group and Ring B is a substituted or unsubstituted phenyl group.

15 23. The method of Claim 22 wherein:

M is >C(OH)R²; and

20 n is two.

24. The method of Claim 23 wherein R² is a substituted or unsubstituted aromatic group.

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25. The method of Claim 23 wherein R² is an aromatic group substituted with halogen.

26. The method of Claim 25 wherein R² is a 4-chlorophenyl group.

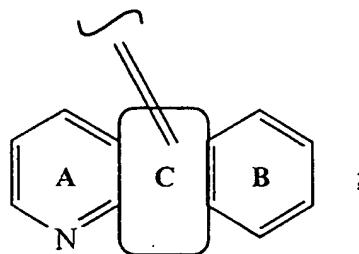
5 27. The method of Claim 22 wherein:

Ring A is a pyridyl group;
n is two;
M is >C(OH)R²; and
R² is a 4-chlorophenyl group.

10 28. The method of Claim 27 wherein X₁ is -CH₂-S- or -CH₂-CH₂-.

29. The method of Claim 27 wherein X₁ is -CH₂-O-.

30. The method of Claim 1 wherein Z is represented by the structural formula:



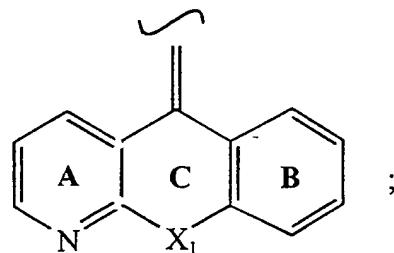
15 wherein:

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Ring C is a substituted or unsubstituted C₆, C₇ or C₈ non-aromatic carbocyclic ring or a substituted or unsubstituted non-aromatic heterocyclic ring; and

5 Ring A and Ring B are independently substituted or unsubstituted.

31. The method of Claim 30 wherein Z is represented by the following structural formula:



10 wherein:

X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-, -O-CH₂-, -CH₂-O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂-, -CH₂-SO-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO- or -CO-NR_c-; wherein:

15 R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

20 Ring A and Ring B are independently substituted or unsubstituted.

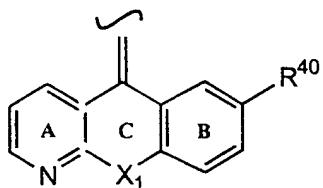
-135-

32. The method of Claim 31 wherein Ring B is substituted with -OH, halogen, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, -(O)_u-(CH₂)_t-C(O)OR²⁰, -(O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²¹R²² or -(O)_u-(CH₂)_t-NHC(O)O-R²⁰; wherein:
5 R²⁰, R²¹ or R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or
10 R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;
15 u is zero or one; and
t is an integer from zero to about 3.

33. The method of Claim 31 wherein
X₁ is -NR_c-CH₂-, -CH₂NR_c-, -NR_c-CO- or -CONR_c-;
20 R_c is -(CH₂)_s-COOR³⁰, -(CH₂)_s-C(O)-NR³¹R³² or -(CH₂)_s-NHC(O)-O-R³⁰;
s is an integer from one to about three;
R³⁰, R³¹ or R³² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or
25 R³¹ and R³², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

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34. The method of Claim 32 wherein Z is represented by the following structural formula:



wherein R⁴⁰ is -OH, halogen, aliphatic group,
 5 substituted aliphatic group, -NR²⁴R²⁵, Q-(aliphatic group), Q-(substituted aliphatic group),
 -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group,
 10 -(O)_u-(CH₂)_t-C(O)OR²⁰, -(O)_u-(CH₂)_t-OC(O)R²⁰,
 -(O)_u-(CH₂)_t-C(O)-NR²¹R²² or -(O)_u-(CH₂)_t-NHC(O)O-R²⁰;
 R²⁰, R²¹ or R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic
 15 heterocyclic group; or
 R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;
 Q is -NR²⁴C(O)- or -NR²⁴S(O)₂-;
 20 R²⁴ and R²⁵ are independently -H, -OH, an aliphatic group or a substituted aliphatic group;
 u is zero or one; and
 t is an integer from zero to about 3.

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35. The method of Claim 34 wherein:

X₁ is -NR_c-CH₂-, -CH₂-NR_c, -NR_c-CO-, or -CO-NR_c-;

R_c is -(CH₂)_s-COOR³⁰, -(CH₂)_s-C(O)-NR³¹R³² or

-(CH₂)_s-NHC(O)-O-R³⁰;

5 R³⁰, R³¹ or R³² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

10 R³¹ and R³², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring; and

s is an integer from one to about three.

36. The method of Claim 34 wherein R⁴⁰ is -O-CH₃.

15 37. The method of Claim 36 wherein R¹ is -OH.

38. The method of Claim 36 wherein M is >C(OH)R² and n is two.

39. The method of Claim 38 wherein R² is a substituted or unsubstituted aromatic group.

20 40. The method of Claim 38 wherein R² is an aromatic group substituted with halogen.

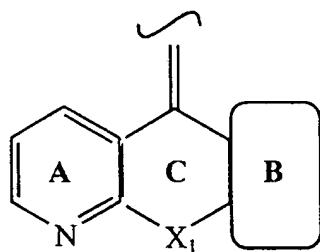
41. The method of Claim 40 wherein R² is a 4-chlorophenyl group.

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42. The method of Claim 41 wherein X_1 is $-\text{CH}_2\text{-O}-$.

43. The method of Claim 41 wherein X_1 is $-\text{CH}_2\text{-S-}$ or
 $-\text{CH}_2\text{-CH}_2\text{-}$.

44. The method of Claim 1 wherein Z is represented by the
5 following structural formula:



wherein:

Ring B is a substituted or unsubstituted aromatic carbocyclic group or heteroaryl group; and

10 X_1 is $-\text{S-}$, $-\text{CH}_2\text{-}$, $-\text{CH}_2\text{-CH}_2\text{-}$, $-\text{CH}_2\text{-S-}$, $-\text{S-CH}_2\text{-}$,
 $-\text{O-CH}_2\text{-}$, $-\text{CH}_2\text{-O-}$, $-\text{NR}_c\text{-CH}_2\text{-}$, $-\text{CH}_2\text{-NR}_c\text{-}$, $-\text{SO-CH}_2\text{-}$,
 $-\text{CH}_2\text{-SO-}$, $-\text{S(O)}_2\text{-CH}_2\text{-}$, $-\text{CH}_2\text{-S(O)}_2\text{-}$, $-\text{CH=CH-}$, $-\text{NR}_c\text{-CO-}$ or
 $-\text{CO-NR}_c\text{-}$; wherein:

15 R_c is an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group.

45. The method of Claim 44 wherein Ring B is substituted with $-\text{OH}$, halogen, $-\text{O-}$ (aliphatic group),

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-O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, -(O)_u-(CH₂)_t-C(O)OR²⁰, -(O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²¹R²² or -(O)_u-(CH₂)_t-NHC(O)O-R²⁰; wherein:

5 R²⁰, R²¹ or R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

10 R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

u is zero or one; and

t is an integer from zero to about three.

15 46. The method of Claim 44 wherein

X₁ is -NR_c-CH₂-, -CH₂-NR_c, -NR_c-CO-, or -CO-NR_c-;

R_c is -(CH₂)_s-COOR³⁰, -(CH₂)_s-C(O)-NR³¹R³² or

-(CH₂)_s-NHC(O)-O-R³⁰;

R³⁰, R³¹ or R³² are independently -H, an aliphatic

20 group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R³¹ and R³², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring; and

25 s is an integer from one to about three.

47. The method of Claim 44 wherein R¹ is -OH.

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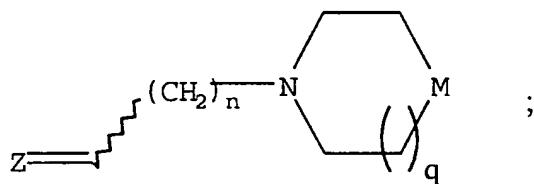
48. The method of Claim 44 wherein M is $>C(OH)R^2$ and n is two.

49. The method of Claim 48 wherein R^2 is a substituted or unsubstituted aromatic group.

5 50. The method of Claim 48 wherein R^2 is an aromatic group substituted with halogen.

51. The method of Claim 50 wherein R^2 is a 4-chlorophenyl group.

52. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation comprising administering to a subject in need thereof an effective amount of a compound represented by the following structural formula:



15 and physiologically acceptable salts thereof, wherein:

n is an integer from one to about four;

M is $>NR^2$ or $>CR^2$;

R^1 is -H, -OH, -N₃, an aliphatic group,

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-O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group),
5 -O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -CN, -COOH, -CO-NR³R⁴ or -NR³R⁴; or R¹ is a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M;

10 R² is -H, -OH, an acyl group, a substituted acyl group, -NR⁵R⁶, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

15 R³, R⁴, R⁵ and R⁶ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

20 R¹ and R², R³ and R⁴, or R⁵ and R⁶ taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic
25 or heterocyclic ring;

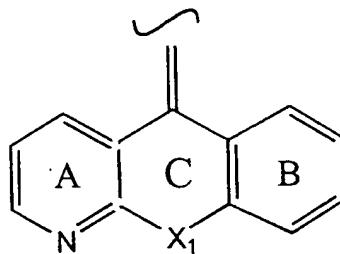
q is zero to three;

the ring containing M is substituted or unsubstituted;

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Z is represented by the following structural formula:

5



wherein:

X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-,
 -O-CH₂-, -CH₂-O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂-,
 -CH₂-SO-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO- or
 10 -CO-NR_c-;

wherein:

R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

15 Ring A and Ring B are independently substituted or unsubstituted.

53. The method of Claim 52 wherein

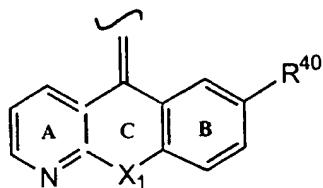
n is two;

20 M is CR¹R²; and

R² is a substituted aromatic group.

54. The method of Claim 53 wherein Z is represented by the following structural formula:

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wherein:

R⁴⁰ is -OH, halogen, aliphatic group, substituted aliphatic group, -NR²⁴R²⁵, Q-(aliphatic group), Q-(substituted aliphatic group), -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, -(O)_u-(CH₂)_t-C(O)OR²⁰, -(O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²¹R²² or -(O)_u-(CH₂)_t-NHC(O)O-R²⁰;

R²⁰, R²¹ or R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

Q is -NR²⁴C(O)- or -NR²⁴S(O)₂-;

R²⁴ and R²⁵ are independently -H, -OH, an aliphatic group or a substituted aliphatic group;

u is zero or one; and

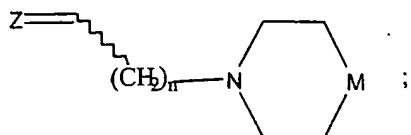
t is an integer from zero to about 3.

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55. The method of Claim 54 wherein
 R^{40} is -O-aliphatic group; and
 R^1 is -OH.

56. The method of Claim 55 wherein X_1 is -CH₂-O-.

5 57. A compound represented by the following structural formula:



and physiologically acceptable salts thereof,
wherein:

10 n is an integer from one to about four;
M is >NR² or >CR¹R²;
R₁ is -H, -OH, -N₃, an aliphatic group,
-O-(aliphatic group), -O-(substituted aliphatic
group), -SH, , -S-(aliphatic group), -S-(substituted
15 aliphatic group), -OC(O)-(aliphatic group),
-O-C(O)-(substituted aliphatic group),
-C(O)O-(aliphatic group), -C(O)O-(substituted
aliphatic group), -CN, -COOH, -CO-NR³R⁴ or -NR³R⁴; or
R¹ is a covalent bond between the ring atom at M and
20 an adjacent carbon atom in the ring which contains M;
and

R² is -H, -OH, an acyl group, a substituted acyl
group, -NR⁵R⁶, an aliphatic group, a substituted
aliphatic group, an aromatic group, a substituted

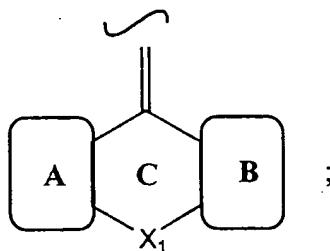
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aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

5 R³, R⁴, R⁵ and R⁶ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

10 R¹ and R², R³ and R⁴, or R⁵ and R⁶ taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring; and

15 Z is represented by the following structural formula:



wherein:

20 Ring A is a substituted or unsubstituted heteroaryl group;

Ring B is a substituted or unsubstituted aromatic carbocyclic or heteroaryl group;

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wherein:

X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-,
-O-CH₂-, -CH₂-O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂-,
-CH₂-SO-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO- or
-CO-NR_c-; wherein:

R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group.

10 58. The compound of Claim 57 wherein:

Ring A or Ring B is substituted with

- (O)_u-(CH₂)_t-C(O)OR²⁰, -(O)_u-(CH₂)_t-OC(O)R²⁰,
- (O)_u-(CH₂)_t-C(O)-NR²¹R²² or - (O)_u-(CH₂)_t-NHC(O)O-R²⁰;
R²⁰, R²¹ and R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

u is zero or one; and

t is an integer from 0 to about 3.

59. The compound of Claim 57 wherein:

R_c is -(CH₂)_s-COOR³⁰, -(CH₂)_s-C(O)-NR³¹R³² or

-(CH₂)_s-NHC(O)-O-R³⁰;

R³⁰, R³¹ and R³² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic

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group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R³¹ and R³², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring; and

5 s is an integer from one to about three.

60. The compound of Claim 57 wherein Ring B is a substituted or unsubstituted heteroaryl group.
- 10 61. The compound of Claim 57 wherein Ring A is a substituted or unsubstituted pyridyl group and Ring B is a substituted or unsubstituted aromatic carbocyclic group.
- 15 62. The compound of Claim 57 wherein Ring A is a substituted or unsubstituted pyridyl group and Ring B is a substituted or unsubstituted heteroaryl group.
63. The compound of Claim 57 wherein R¹ is -H or -OH.
64. The compound of Claim 57 wherein M is >C(OH)R² and n is two.
- 20 65. The compound of Claim 64 wherein R² is an aromatic or substituted aromatic group.
66. The compound of Claim 64 wherein R² is an aromatic group substituted with halogen.

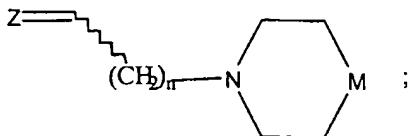
-148-

67. The compound of Claim 66 wherein R² is a 4-chlorophenyl group.
68. The compound of Claim 57 wherein Ring A is a substituted or unsubstituted heteroaryl group and
5 Ring B is a substituted or unsubstituted phenyl group.
69. The compound of Claim 68 wherein:
n is two; and
M is >C(OH)R².
- 10 70. The compound of Claim 69 wherein R² is a substituted or unsubstituted aromatic group.
71. The compound of Claim 69 wherein R² is an aromatic group that is substituted with a halogen.
- 15 72. The compound of Claim 71 wherein R² is a 4-chlorophenyl group.
73. The compound of Claim 68 wherein:
Ring A is a pyridyl group;
n is two;
20 M is >C(OH)R²; and
R² is a 4-chlorophenyl group.
74. The compound of Claim 73 wherein X₁ is -CH₂-S- or -CH₂-CH₂-.

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75. The compound of Claim 73 wherein X₁ is -CH₂-O-.

76. A compound represented by the following structural formula:



5 and physiologically acceptable salts thereof,
wherein:

n is an integer from one to about four;

M is >NR² or >CR¹R²;

R¹ is -H, -OH, -N₃, an aliphatic group,

10 -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -CN, -COOH, -CO-NR³R⁴ or -NR³R⁴; or
15 R¹ is a covalent bond between the ring atom M and an adjacent carbon atom in the ring which contains M;

20 R² is -H, -OH, an acyl group, a substituted acyl group, -NR⁵R⁶, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

25 R³, R⁴, R⁵ and R⁶ are independently -H, an acyl group, a substituted acyl group, an aliphatic group,

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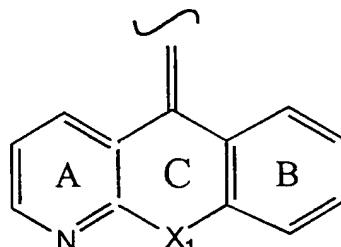
a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

5

R^1 and R^2 , R^3 and R^4 , or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring; and

10

Z is represented by the following structural formula:



15

wherein:

X_1 is $-S-$, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$, $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, $-CH=CH-$, $-NR_c-CO-$ or $-CO-NR_c-$; wherein:

20

R_c is $-H$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

25

Ring A and Ring B are independently substituted or unsubstituted.

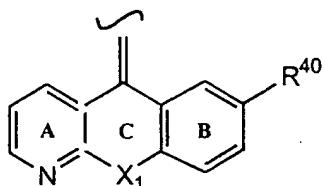
-151-

77. The compound of Claim 76 wherein Ring B is substituted with -OH, halogen, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, -(O)_u-(CH₂)_t-C(O)OR²⁰, -(O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²¹R²² or -(O)_u-(CH₂)_t-NHC(O)O-R²⁰; wherein:
5 R²⁰, R²¹ or R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or
10 R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;
15 u is zero or one; and
t is an integer from zero to about three.

78. The compound of Claim 76 wherein
X₁ is -NR_c-CH₂-, -CH₂-NR_c, -NR_c-CO-, or -CO-NR_c;
R_c is -(CH₂)_s-COOR³⁰, -(CH₂)_s-C(O)-NR³¹R³² or
20 -(CH₂)_s-NHC(O)-O-R³⁰;
R³⁰, R³¹ or R³² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group); or
25 R³¹ and R³², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring; and
s is an integer from one to about three.

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79. The compound of Claim 76 wherein Z is represented by the following structural formula:



wherein:

- 5 R⁴⁰ is -OH, halogen, aliphatic group, substituted aliphatic group, -NR²⁴R²⁵, Q-(aliphatic group), Q-(substituted aliphatic group), -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group),
10 an electron withdrawing group, -(O)_u-(CH₂)_t-C(O)OR²⁰, -(O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²¹R²² or
- (O)_u-(CH₂)_t-NHC(O)O-R²⁰;
15 R²⁰, R²¹ or R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or
R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;
20 Q is -NR²⁴C(O)- or -NR²⁴S(O)₂-;
R²⁴ and R²⁵ are independently -H, -OH, an aliphatic group or a substituted aliphatic group;
u is zero or one; and
t is an integer from zero to about 3.

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80. The compound of Claim 79 wherein

X₁ is -NR_c-CH₂-, -CH₂-NR_c, -NR_c-CO-, or -CO-NR_c-;

R_c is -(CH₂)_s-COOR³⁰, -(CH₂)_s-C(O)-NR³¹R³² or

-(CH₂)_s-NHC(O)-O-R³⁰;

5 R³⁰, R³¹ or R³² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

10 R³¹ and R³², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring; and

s is an integer from one to about 3.

81. The compound of Claim 80 wherein R⁴⁰ is -O-CH₃.

82. The compound of Claim 81 wherein R¹ is -OH.

15 83. The compound of Claim 81 wherein M is >C(OH)R² and n is two.

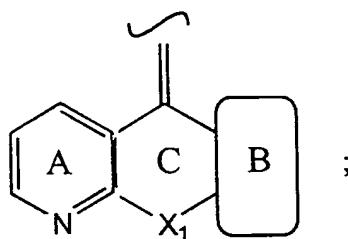
84. The compound of Claim 83 wherein R² is a substituted or unsubstituted aromatic group.

20 85. The compound of Claim 83 wherein R² is an aromatic group substituted with halogen.

86. The compound of Claim 85 wherein R² is a 4-chlorophenyl group.

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87. The compound of Claim 86 wherein X_1 is $-\text{CH}_2\text{-O}-$.
88. The compound of Claim 86 wherein X_1 is $-\text{CH}_2\text{-S-}$ or
 $-\text{CH}_2\text{-CH}_2\text{-}$.
89. The compound of Claim 57 wherein Z is represented by
5 the following structural formula:



wherein:

Ring B is a substituted or unsubstituted aromatic carbocyclic group or heteroaryl group; and

10 X_1 is $-\text{S-}$, $-\text{CH}_2\text{-}$, $-\text{CH}_2\text{-CH}_2\text{-}$, $-\text{CH}_2\text{-S-}$, $-\text{S-CH}_2\text{-}$,
 $-\text{O-CH}_2\text{-}$, $-\text{CH}_2\text{-O-}$, $-\text{NR}_c\text{-CH}_2\text{-}$, $-\text{CH}_2\text{-NR}_c\text{-}$, $-\text{SO-CH}_2\text{-}$,
 $-\text{CH}_2\text{-SO-}$, $-\text{S(O)}_2\text{-CH}_2\text{-}$, $-\text{CH}_2\text{-S(O)}_2\text{-}$, $-\text{CH=CH-}$, $-\text{NR}_c\text{-CO-}$ or
 $-\text{CO-NR}_c\text{-}$; wherein:

15 R_c is $-\text{H}$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group.

90. The compound of Claim 89 wherein Ring B is
20 substituted with $-\text{OH}$, a halogen, $-\text{O-}$ (aliphatic group), $-\text{O-}$ (substituted aliphatic group),

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-O-(aromatic group), -O-(substituted aromatic group),
an electron withdrawing group, -(O)_u-(CH₂)_t-C(O)OR²⁰,
-(O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²¹R²² or
-(O)_u-(CH₂)_t-NHC(O)O-R²⁰; wherein:

5 R²⁰, R²¹ or R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

10 R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

u is zero or one; and

t is an integer from zero to about three.

91. The compound of Claim 89 wherein

15 X₁ is -NR_c-CH₂-, -CH₂-NR_c, -NR_c-CO-, or -CO-NR_c-;
R_c is -(CH₂)_s-COOR³⁰, -(CH₂)_s-C(O)-NR³¹R³² or
-(CH₂)_s-NHC(O)O-R³⁰;

20 R³⁰, R³¹ or R³² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R³¹ and R³², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring; and

25 s is an integer from one to about three.

92. The compound of Claim 89 wherein R¹ is -OH.

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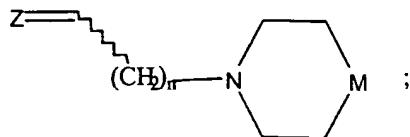
93. The compound of Claim 89 wherein M is $>C(OH)R^2$ and n is two.

94. The compound of Claim 93 wherein R² is a substituted or unsubstituted aromatic group.
5

95. The compound of Claim 93 wherein R² is an aromatic group substituted with halogen.

96. The compound of Claim 95 wherein R² is a 4-chlorophenyl group.

10 97. A compound represented by the following structural formula:



and physiologically acceptable salts thereof,
wherein:

15 n is an integer from one to about four;
 M is $>NR^2$ or $>CR^1R^2$;
 R¹ is -H, -OH, -N₃, an aliphatic group,
-O-(aliphatic group), -O-(substituted aliphatic
group), -SH, , -S-(aliphatic group), -S-(substituted
20 aliphatic group), -OC(O)-(aliphatic group),
-O-C(O)-(substituted aliphatic group),
-C(O)O-(aliphatic group), -C(O)O-(substituted
aliphatic group), -CN, -COOH, -CO-NR³R⁴ or -NR³R⁴; or

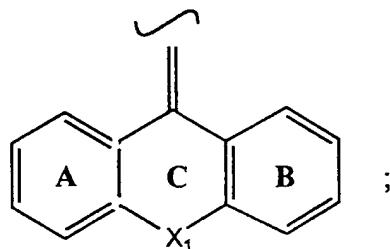
-157-

R^1 is a covalent bond between the ring atom M and an adjacent carbon atom in the ring which contains M;

R^2 is -H, -OH, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; and

Z is represented by the following structural

formula:



wherein:

X_1 is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-, -O-CH₂-, -CH₂-O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂-, -CH₂-SO-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO- or -CO-NR_c;

R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

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98. The compound of Claim 97 wherein Ring A or Ring B has at least two substituents.

99. The compound of Claim 97 wherein Ring A or Ring B is substituted with -OH, a halogen, -O-(aliphatic

5 group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$; wherein:

10 R^{20} , R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

15 R^{21} and R^{22} , taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

u is zero or one; and

t is an integer from zero to about three.

100. The compound of Claim 97 wherein

20 X_1 is $-NR_c-CH_2-$, $-CH_2-NR_c$, $-NR_c-CO-$, or $-CO-NR_c-$;

R_c is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or

$-(CH_2)_s-NHC(O)-O-R^{30}$;

25 R^{30} , R^{31} or R^{32} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

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R^{31} and R^{32} , taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring; and
 s is an integer from one to about three.

5 101. The compound of Claim 97 wherein:

n is two;
 M is $>C(OH)R^2$; and
 R^2 is a substituted or unsubstituted aromatic group.

10 102. The compound of Claim 101 wherein R^2 is an aromatic group substituted with halogen.

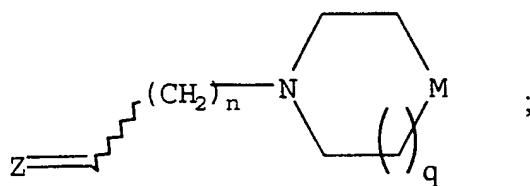
103. The compound of Claim 102 wherein R^2 is a 4-chlorophenyl group.

104. The compound of Claim 103 wherein X_1 is $-CH_2-S-$ or
15 $-CH_2-CH_2-$.

105. The compound of Claim 103 wherein X_1 is $-CH_2-O-$.

106. A compound represented by the following structural formula:

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and physiologically acceptable salts thereof,

wherein:

n is an integer from one to about four;

5 M is >NR² or >CR¹R²;

R¹ is -H, -OH, -N₃, an aliphatic group,
-O-(aliphatic group), -O-(substituted aliphatic
group), -SH, -S-(aliphatic group), -S-(substituted
aliphatic group), -OC(O)-(aliphatic group),

10 -O-C(O)-(substituted aliphatic group),
-C(O)O-(aliphatic group), -C(O)O-(substituted
aliphatic group), -CN, -COOH, -CO-NR³R⁴ or -NR³R⁴; or
R¹ is a covalent bond between the ring atom at M and
an adjacent carbon atom in the ring which contains M;

15 R² is -H, -OH, an acyl group, a substituted acyl
group, -NR⁵R⁶, an aliphatic group, a substituted
aliphatic group, an aromatic group, a substituted
aromatic group, a benzyl group, a substituted benzyl
group, a non-aromatic heterocyclic group or a
20 substituted non-aromatic heterocyclic group; wherein:

25 R³, R⁴, R⁵ and R⁶ are independently -H, an acyl
group, a substituted acyl group, an aliphatic group,
a substituted aliphatic group, an aromatic group, a
substituted aromatic group, a benzyl group, a
substituted benzyl group, a non-aromatic heterocyclic

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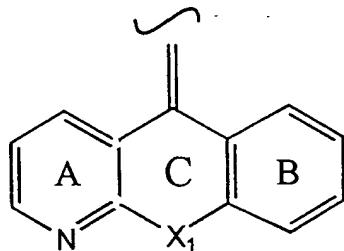
group or a substituted non-aromatic heterocyclic group; or

R¹ and R², R³ and R⁴, or R⁵ and R⁶ taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

q is zero to three;

the ring containing M is substituted or unsubstituted;

Z is represented by the following structural formula:



wherein:

X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-, -O-CH₂-, -CH₂-O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂-, -CH₂-SO-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO- or -CO-NR_c;

wherein:

R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

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Ring A and Ring B are independently substituted or unsubstituted.

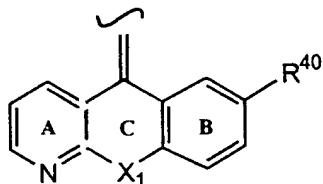
107. The compound of Claim 106 wherein

n is two;

5 M is CR¹R²; and

R² is a substituted aromatic group.

108. The compound of Claim 107 wherein Z is represented by the following structural formula:



10 wherein:

R⁴⁰ is -OH, halogen, aliphatic group, substituted aliphatic group, -NR²⁴R²⁵, Q-(aliphatic group), Q-(substituted aliphatic group), -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, -(O)_u-CH₂)_tC(O)OR²⁰, -(O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²¹R²² or -(O)_u-(CH₂)_t-NHC(O)O-R²⁰;

15 R²⁰, R²¹ or R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or R²¹ and R²², taken together with

20

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the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

Q is -NR²⁴C(O)- or -NR²⁴S(O)₂-;

R²⁴ and R²⁵ are independently -H, -OH, an aliphatic group or a substituted aliphatic group;

5 u is zero or one; and

t is an integer from zero to about 3.

109. The compound of Claim 108 wherein

R⁴⁰ is -O-aliphatic group; and

10 R¹ is -OH.

110. The compound of Claim 109 wherein X₁ is -CH₂-O-.

111. A method of antagonizing a chemokine receptor in a mammal in need thereof comprising administering a compound of Claim 52.

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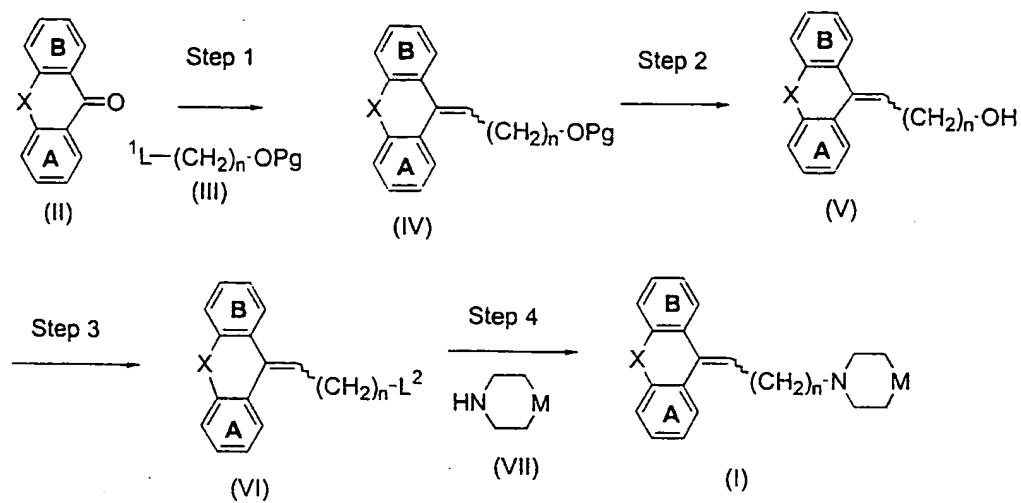


Figure 1

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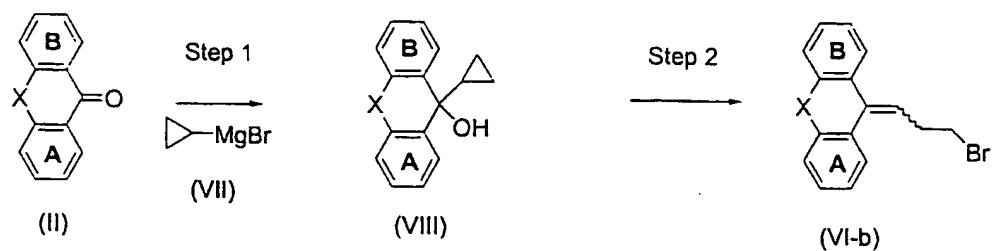


Figure 2

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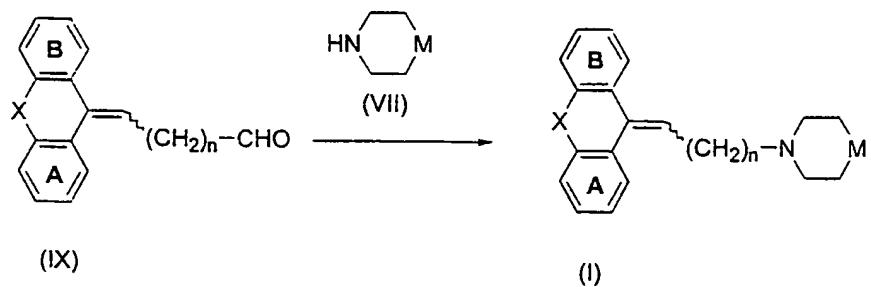


Figure 3

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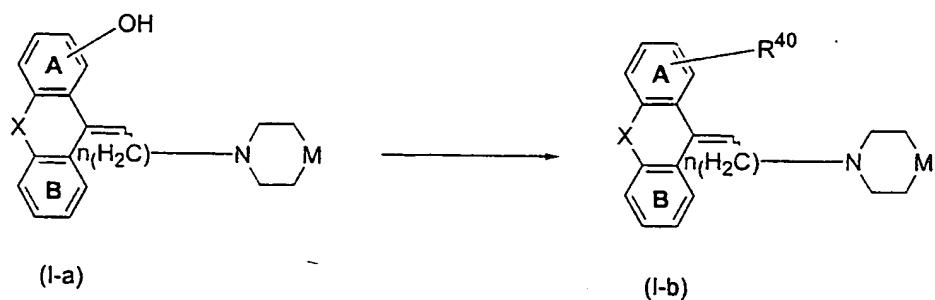


Figure 4

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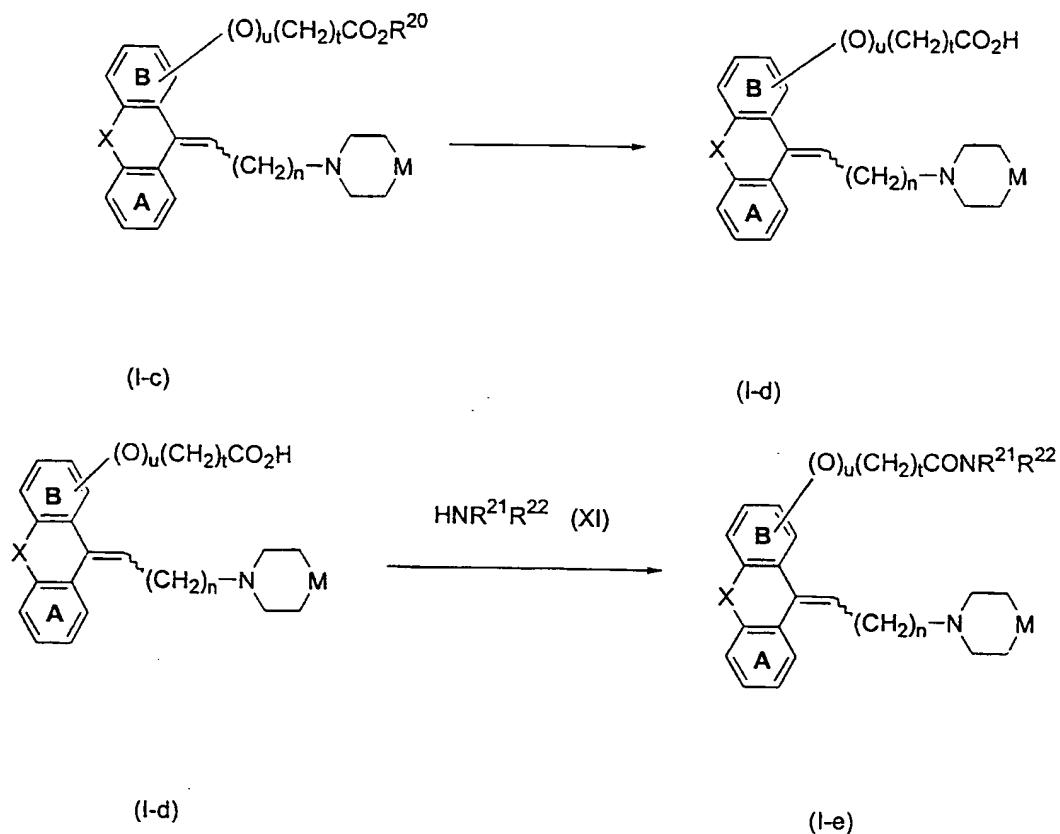


Figure 5

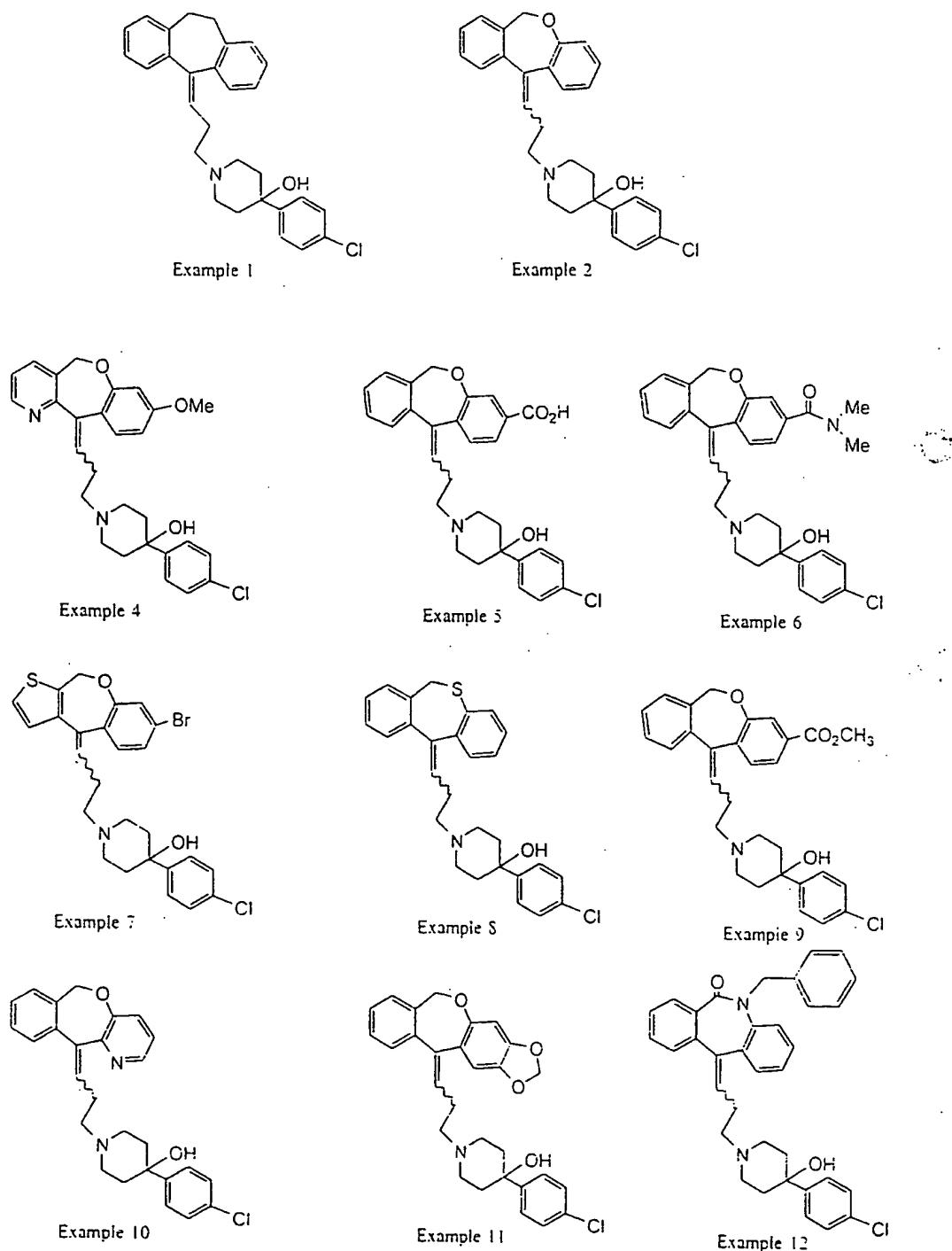


Figure 6A

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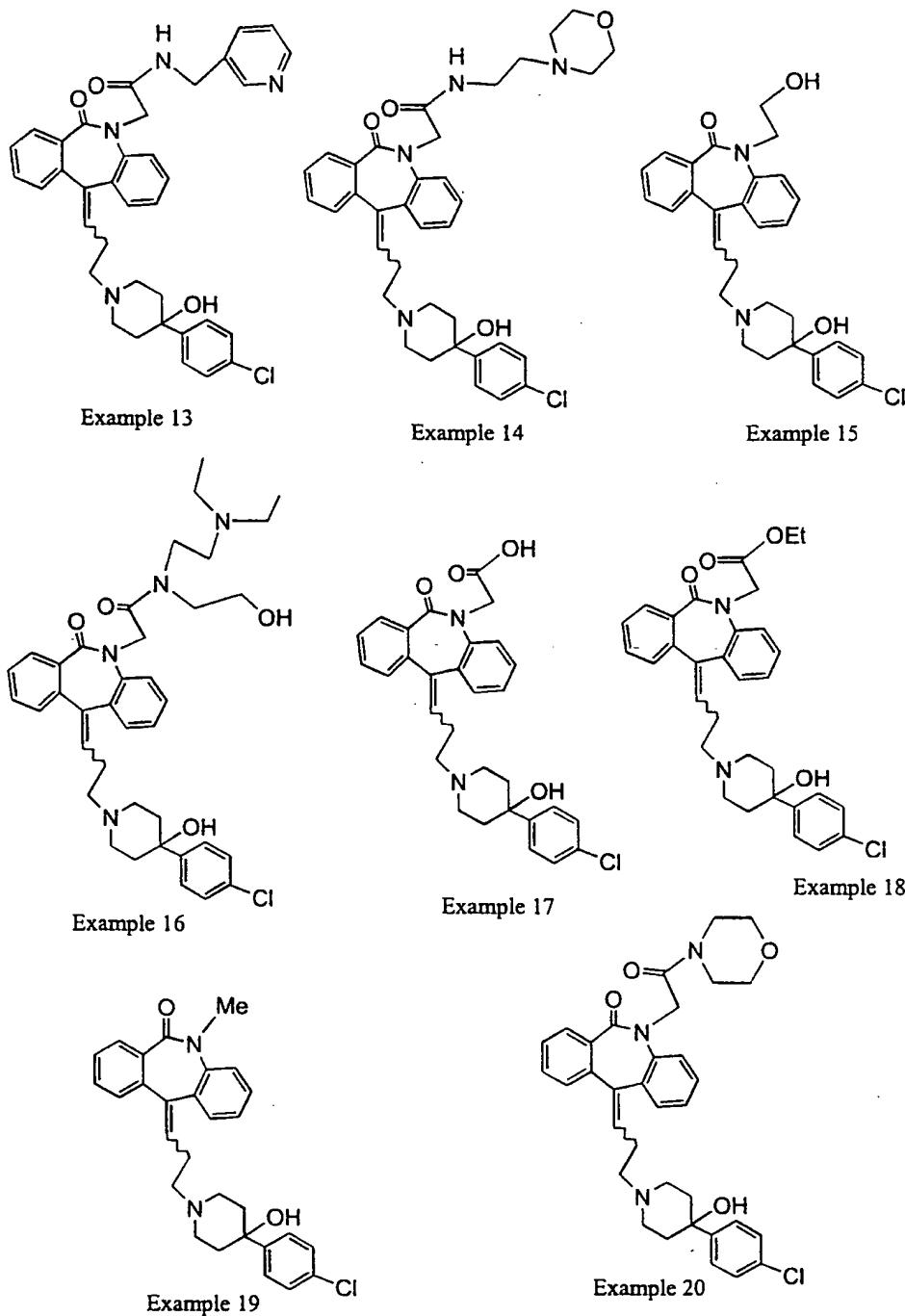


Figure 6B

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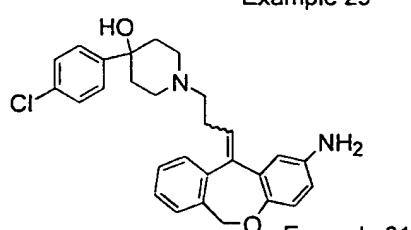
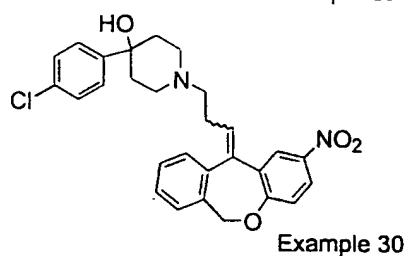
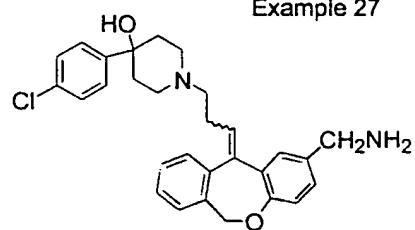
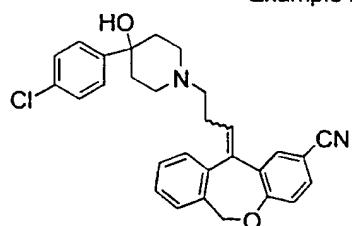
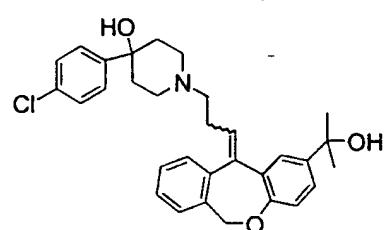
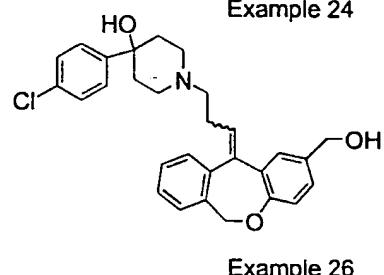
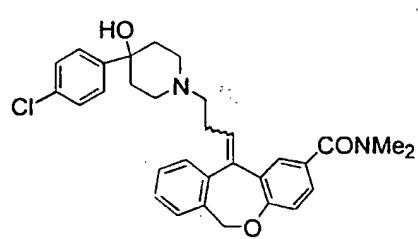
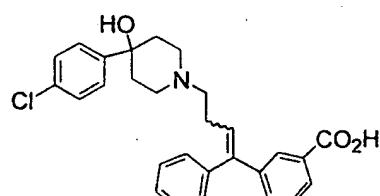
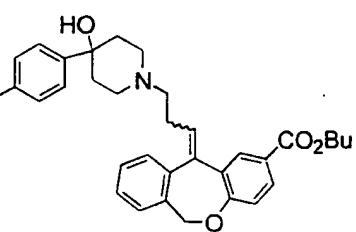
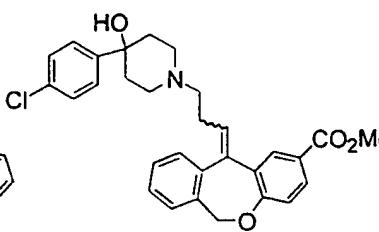
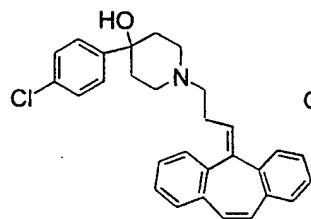
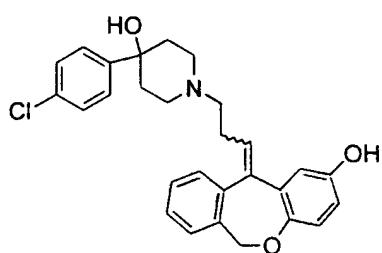
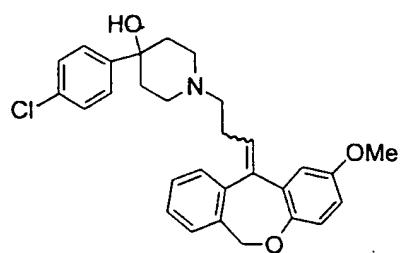


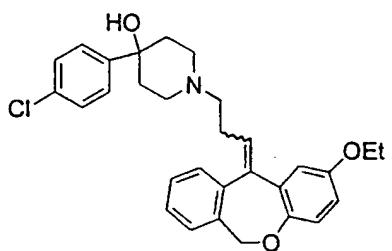
Figure 6C



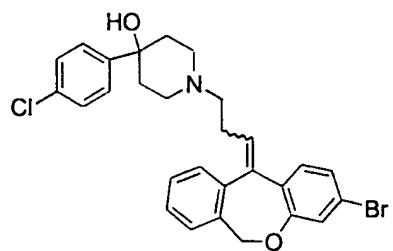
Example 32



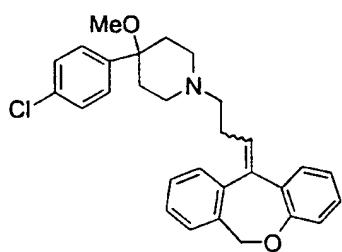
Example 33



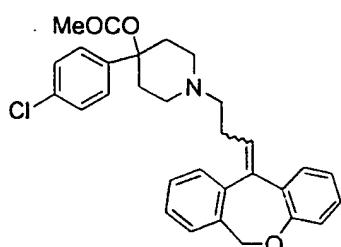
Example 34



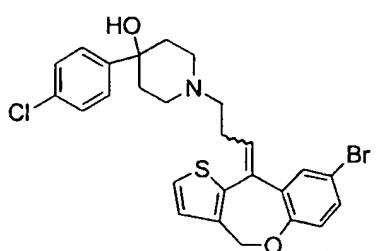
Example 35



Example 36



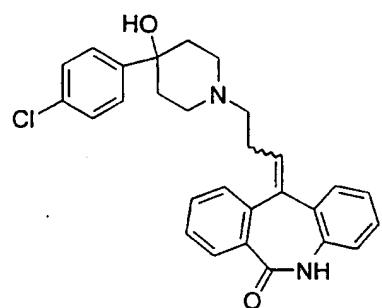
Example 37



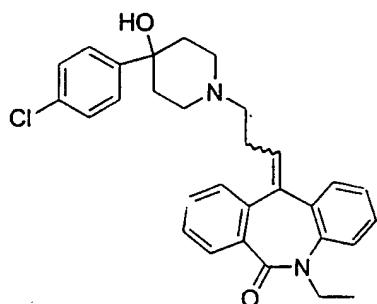
Example 38

Figure 6D

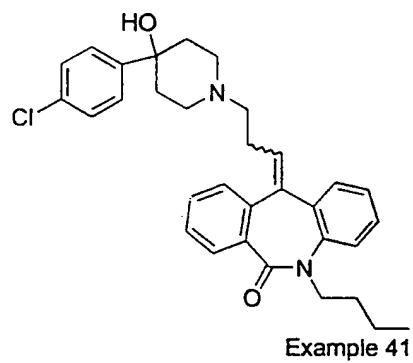
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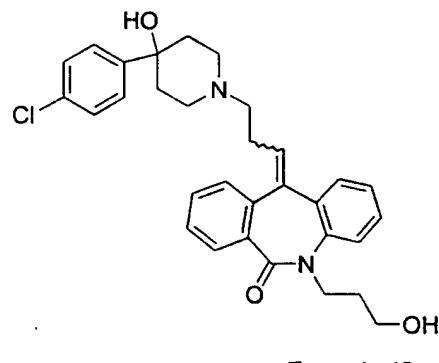
Example 39



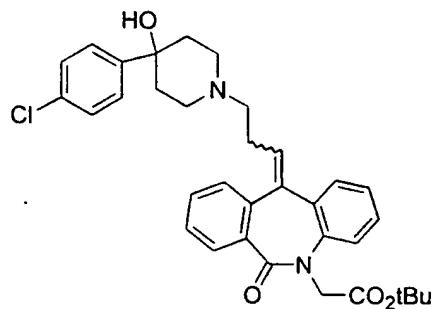
Example 40



Example 41

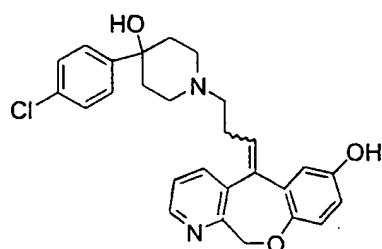


Example 42

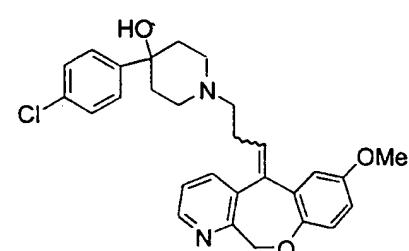


Example 43

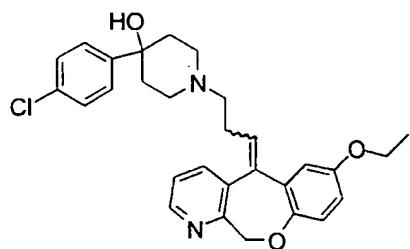
Figure 6E



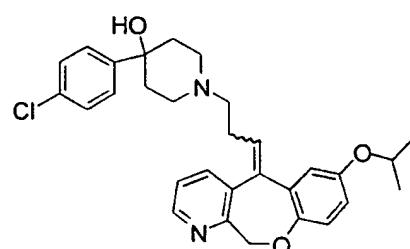
Example 44



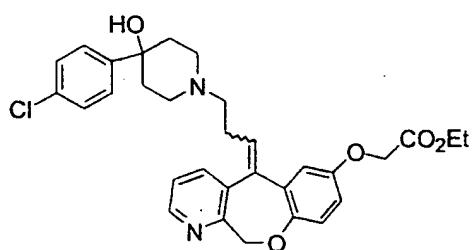
Example 45



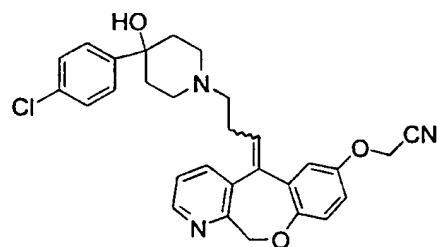
Example 46



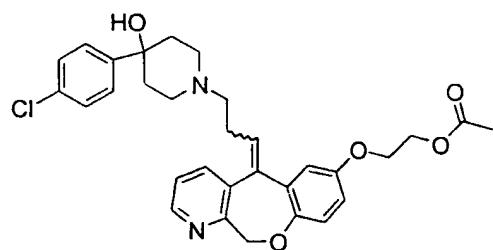
Example 47



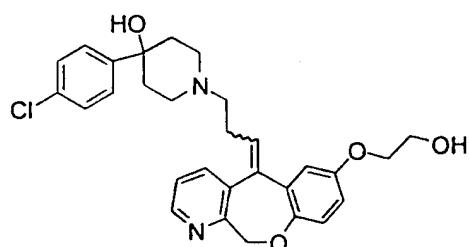
Example 48



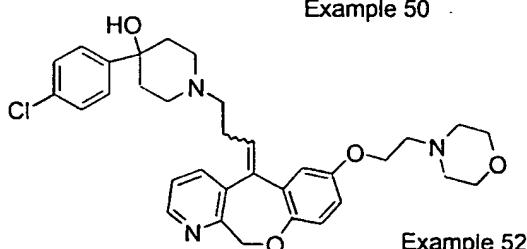
Example 49



Example 50



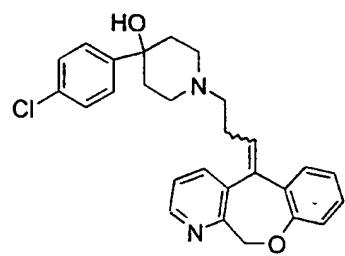
Example 51



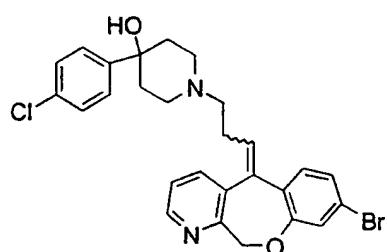
Example 52

Figure 6F

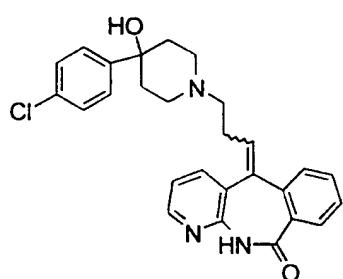
12/32



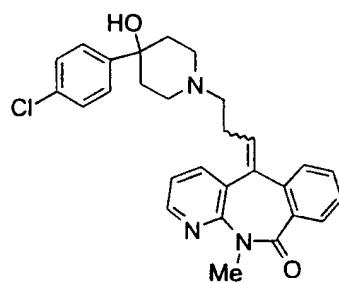
Example 53



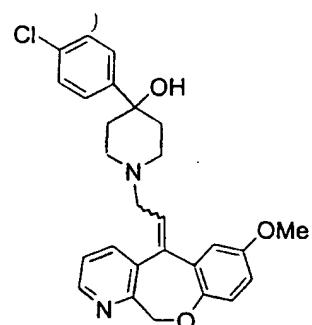
Example 54



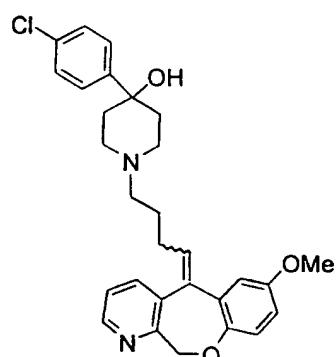
Example 55



Example 56



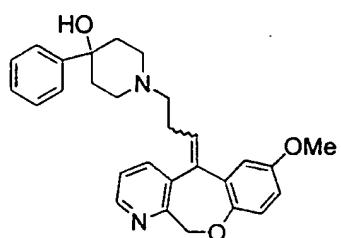
Example 57



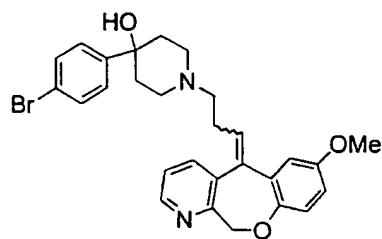
Example 58

Figure 6G

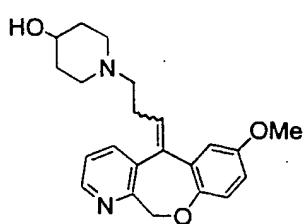
13/32



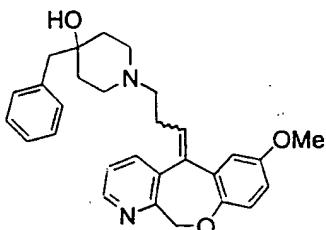
Example 59



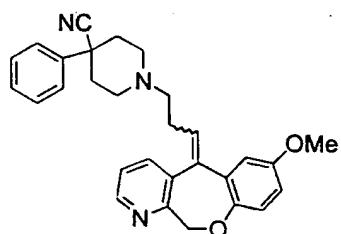
Example 60



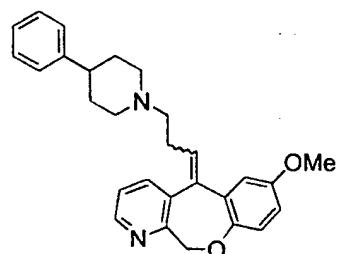
Example 61



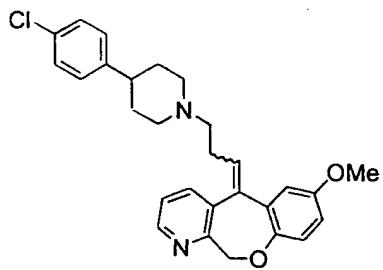
Example 62



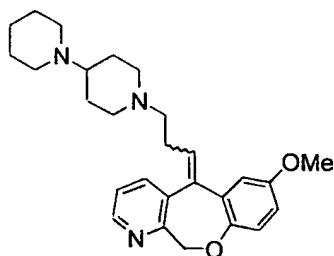
Example 63



Example 64



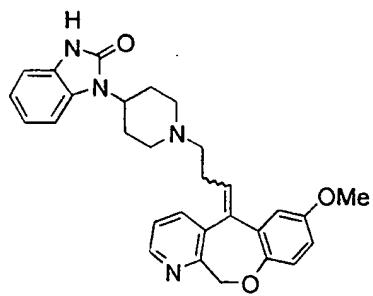
Example 65



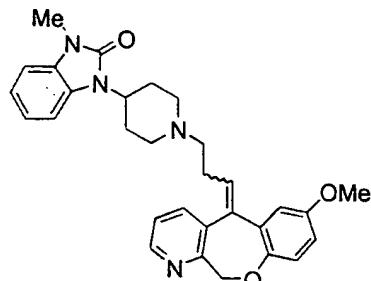
Example 66

Figure 6H

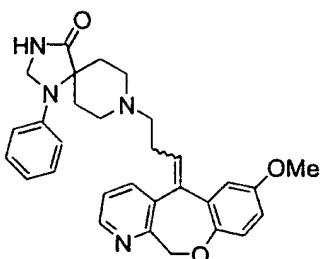
14/32



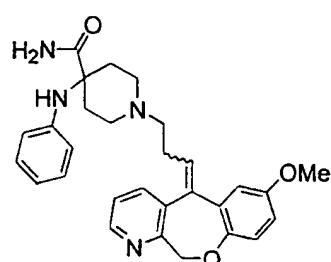
Example 67



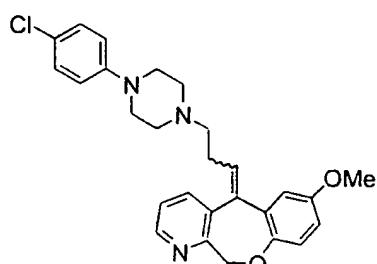
Example 68



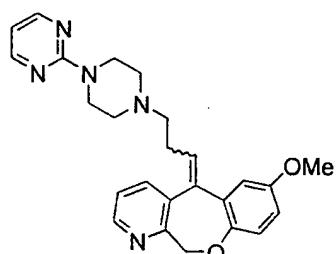
Example 69



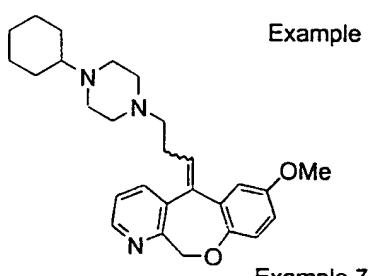
Example 70



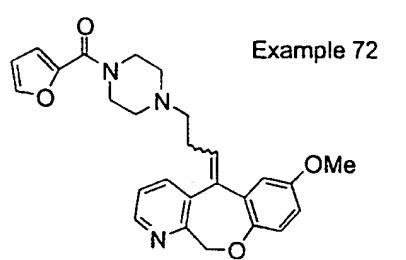
Example 71



Example 72



Example 73



Example 74

Figure 6I

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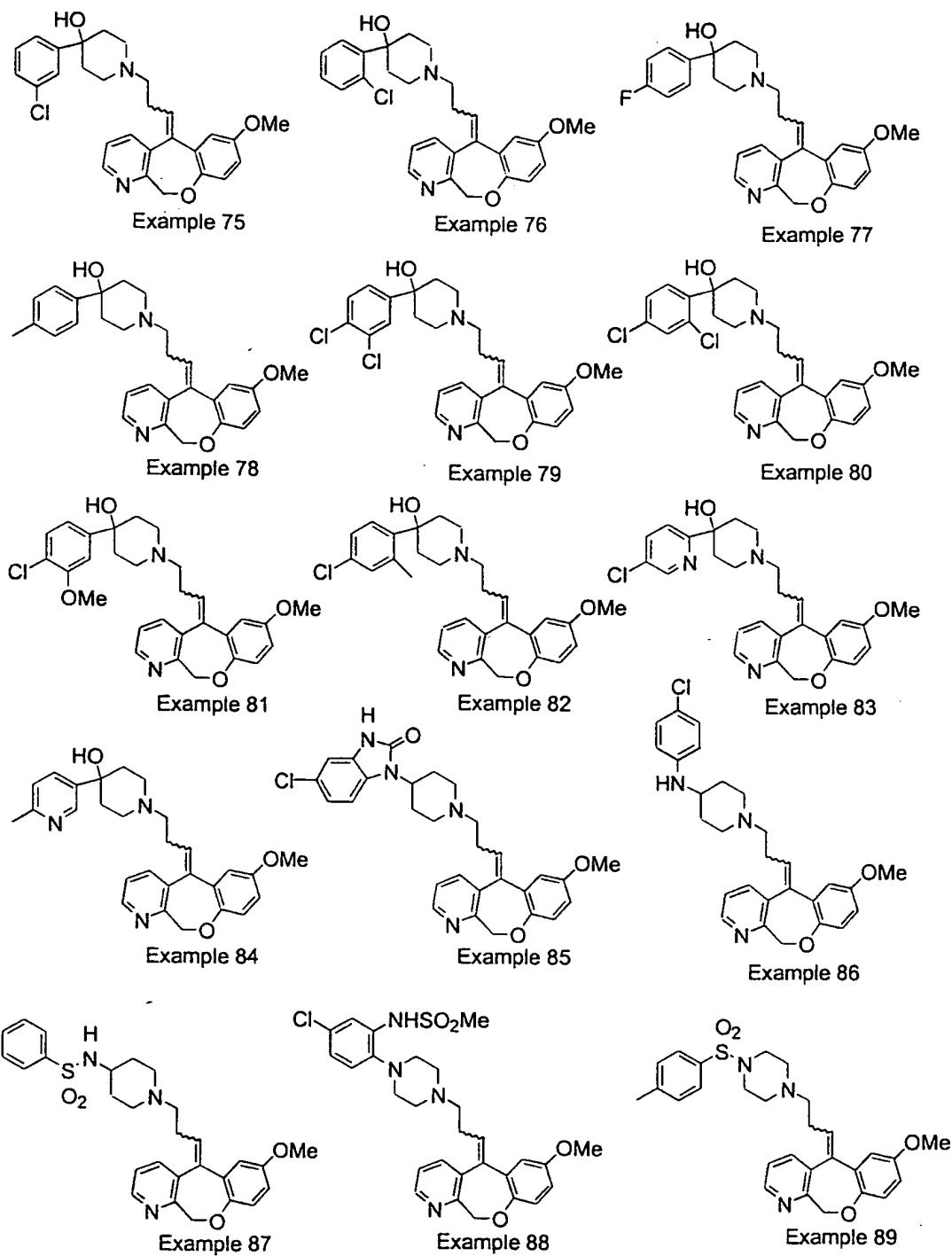


Figure 6J

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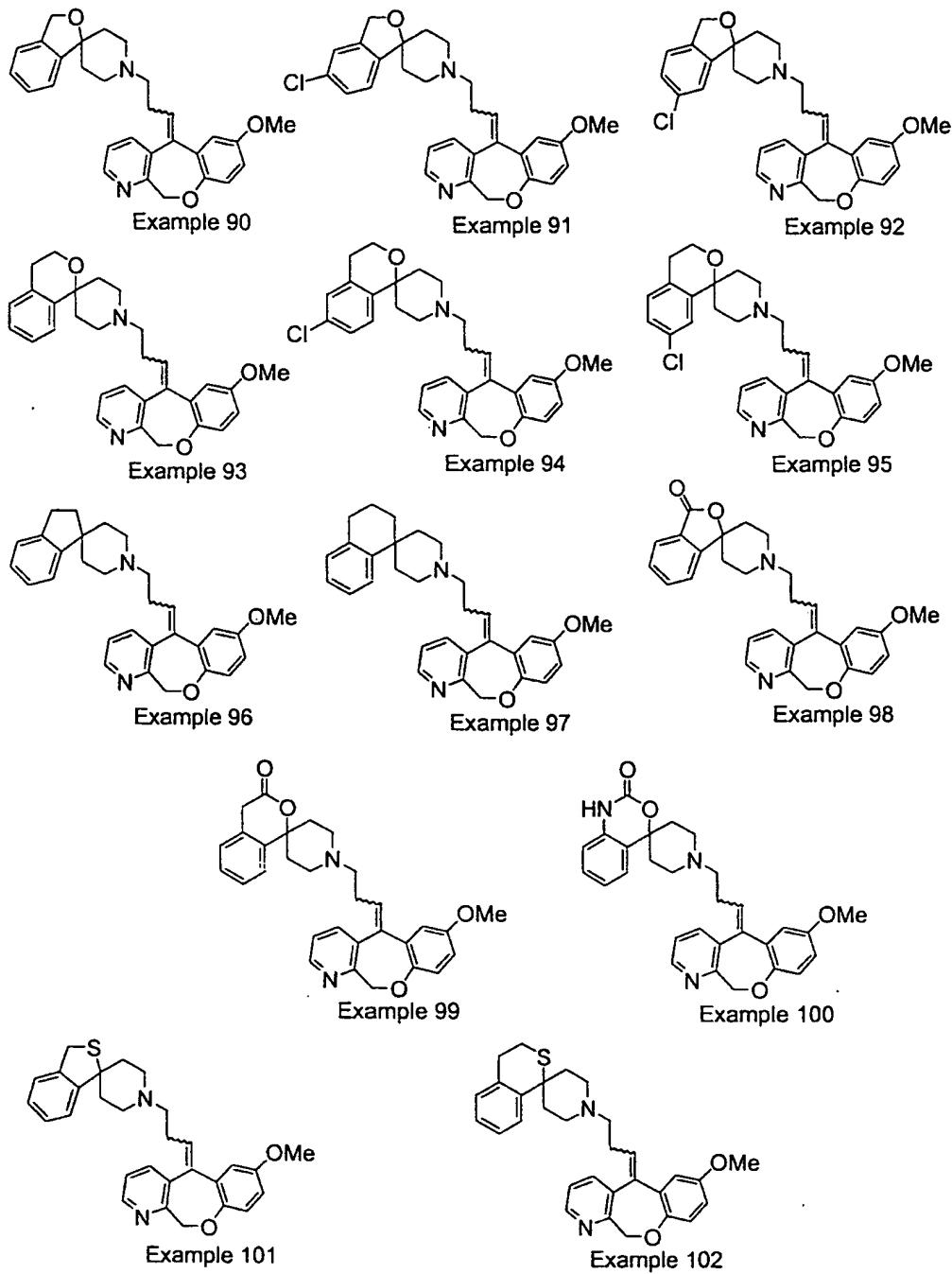


Figure 6K

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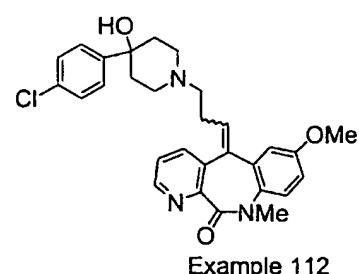
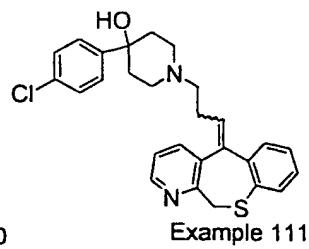
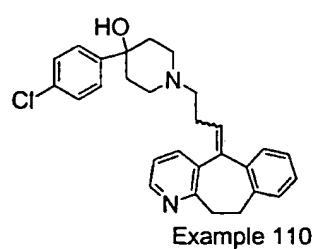
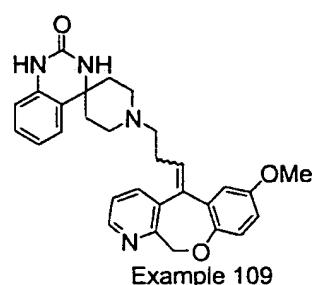
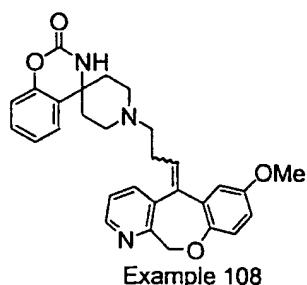
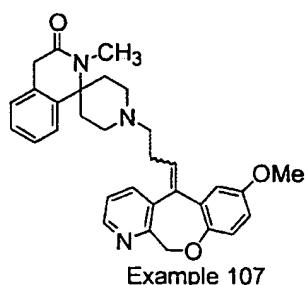
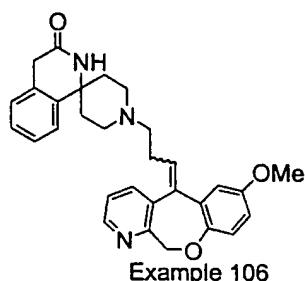
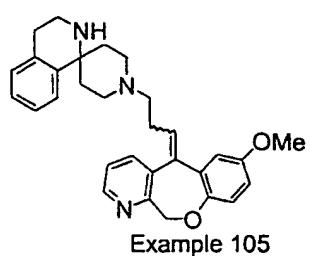
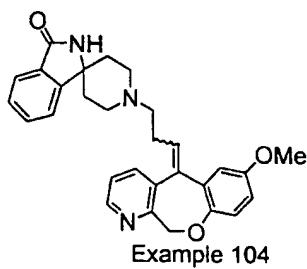
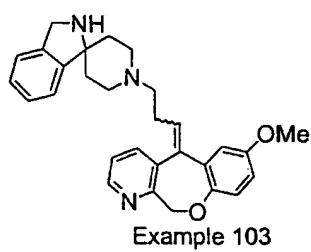


Figure 6L

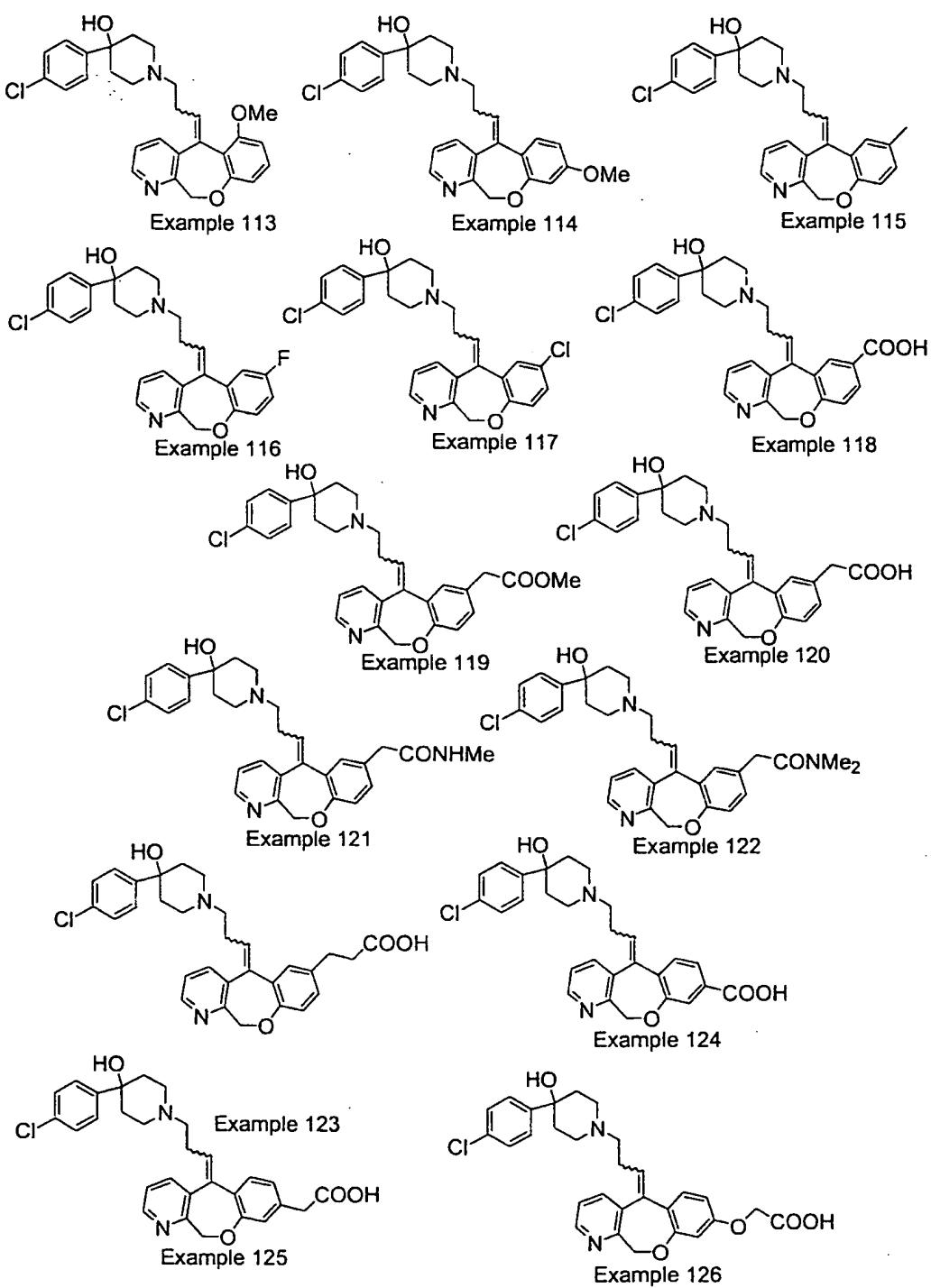


Figure 6M

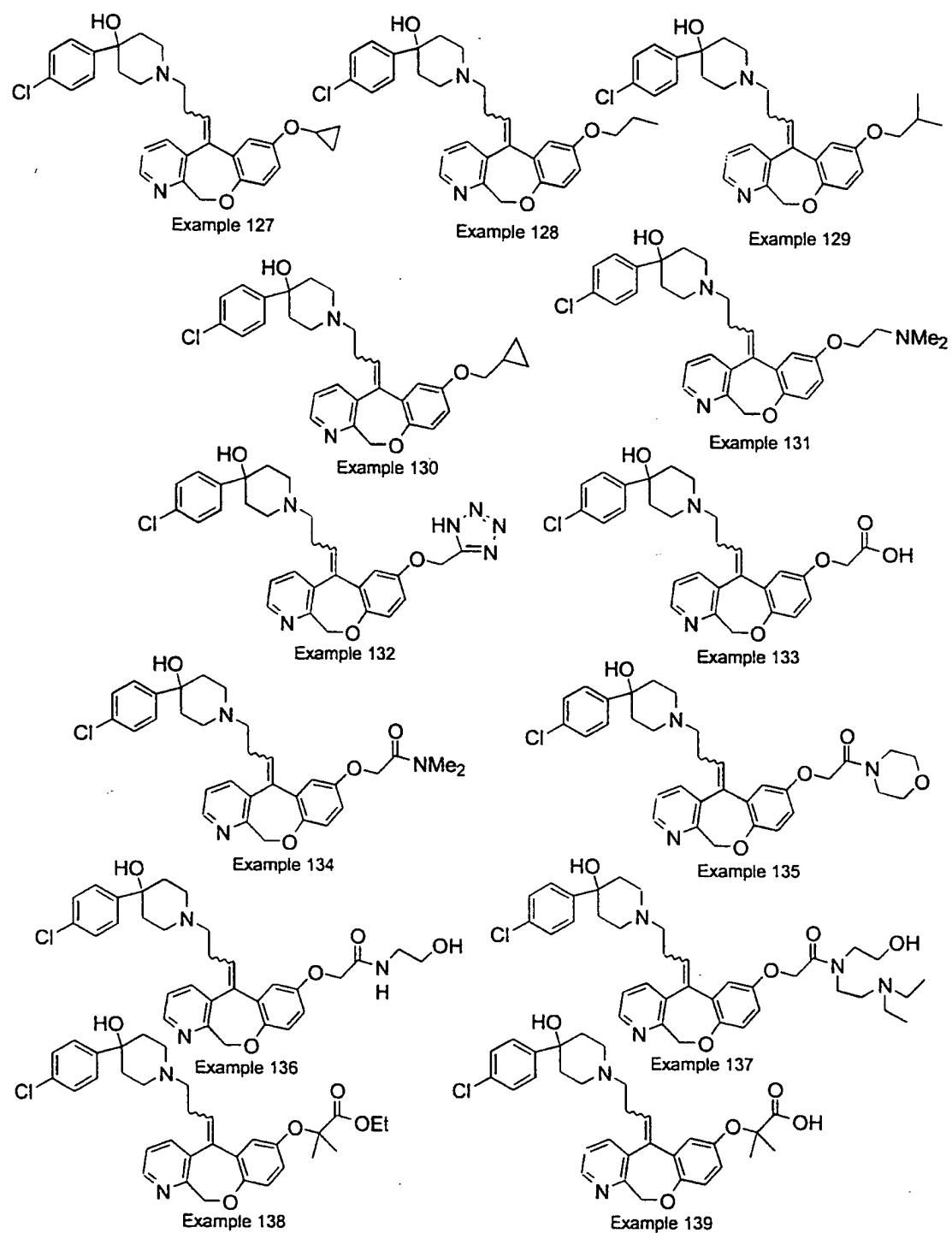


Figure 6N

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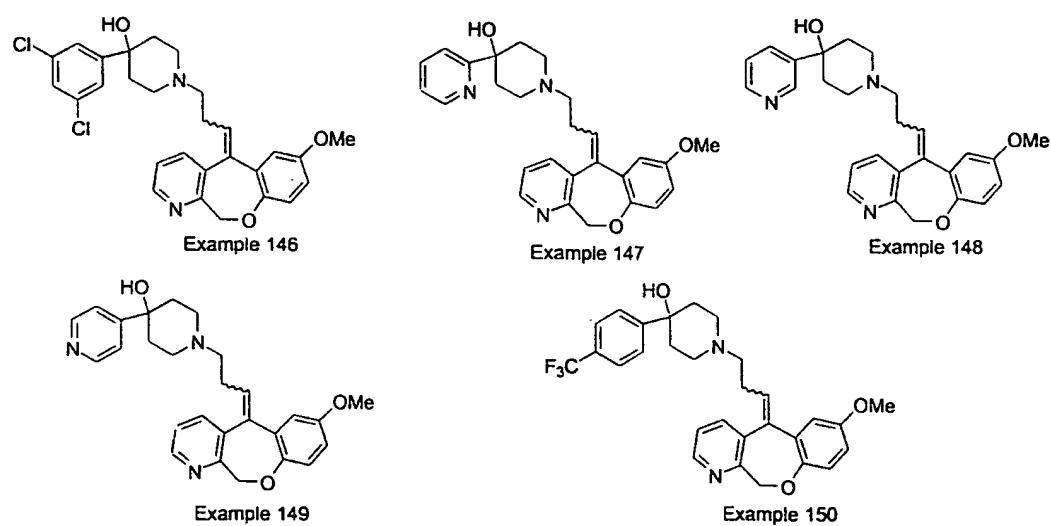
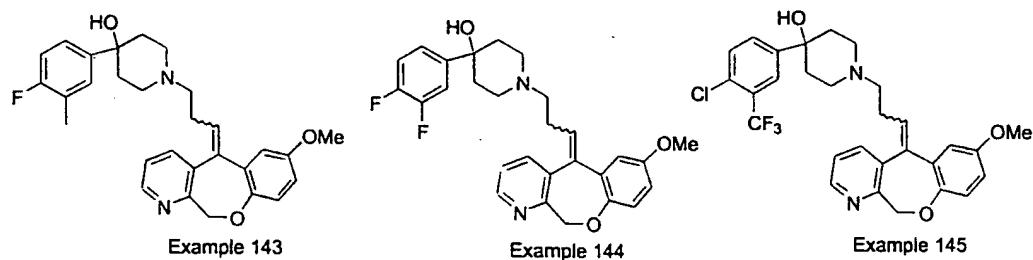
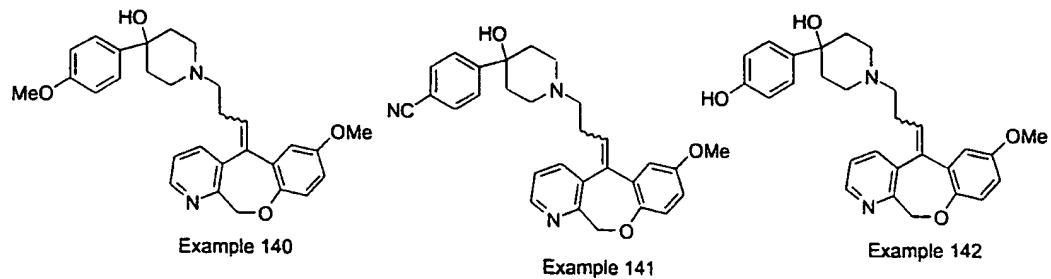


Figure 60

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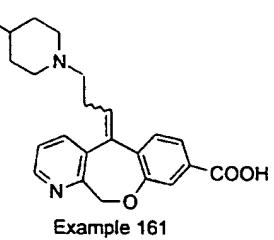
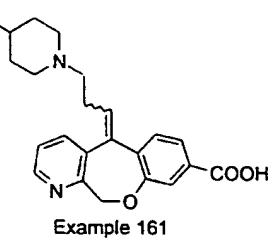
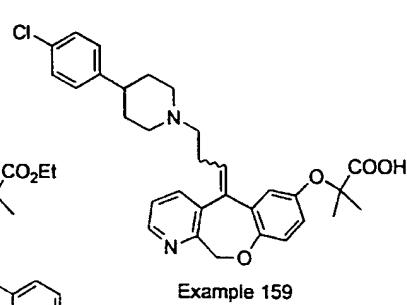
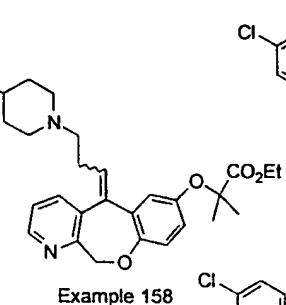
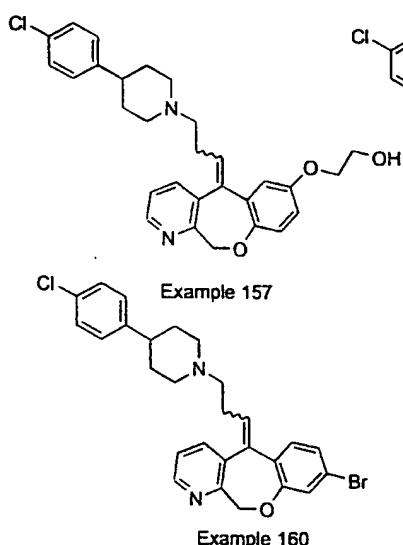
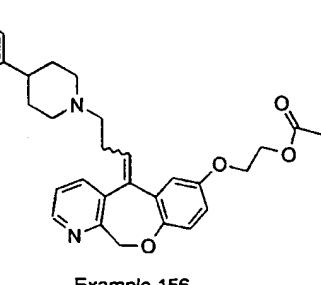
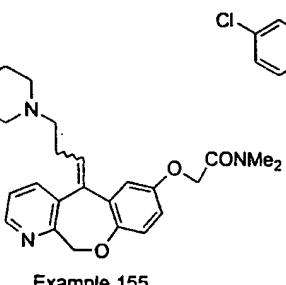
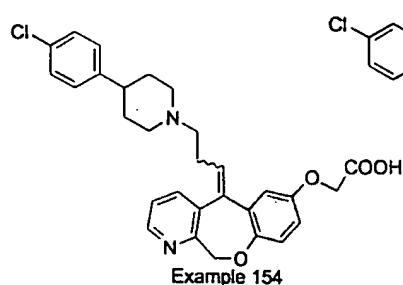
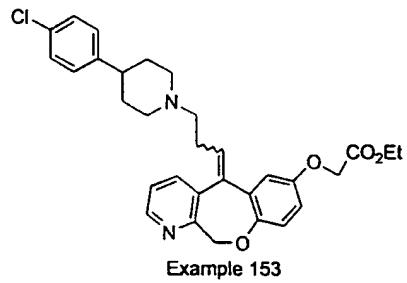
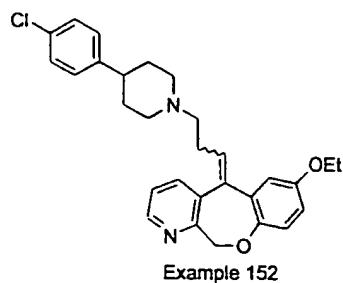
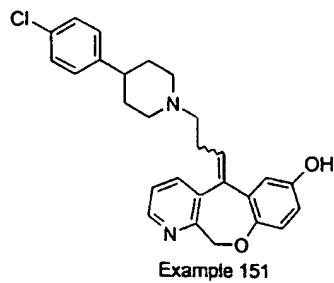


Figure 6P

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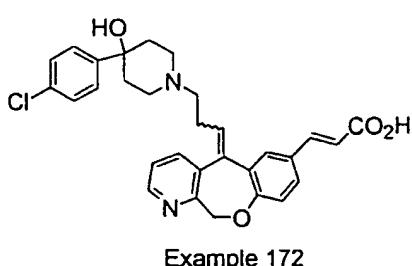
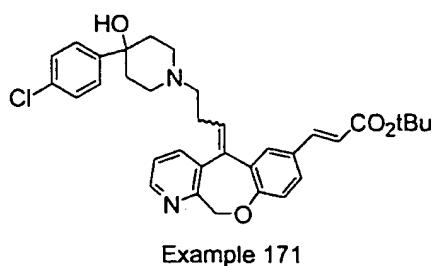
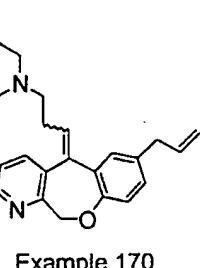
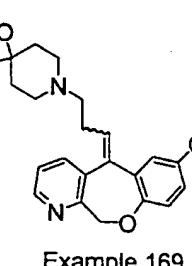
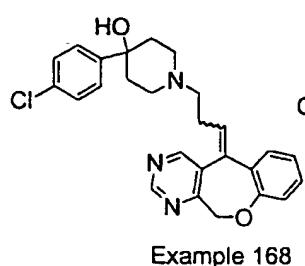
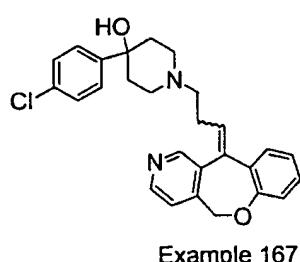
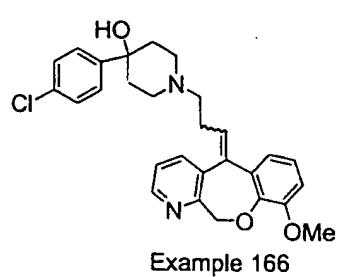
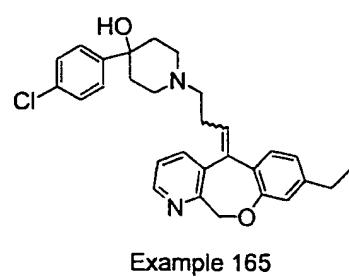
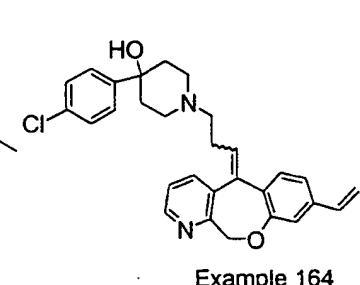
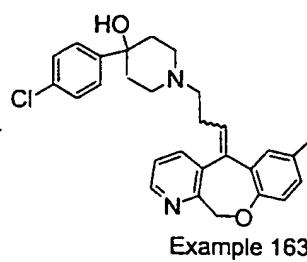
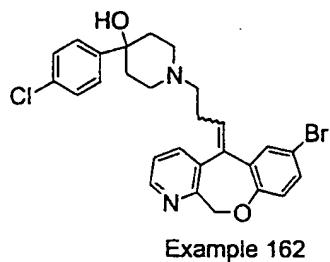


Figure 6Q

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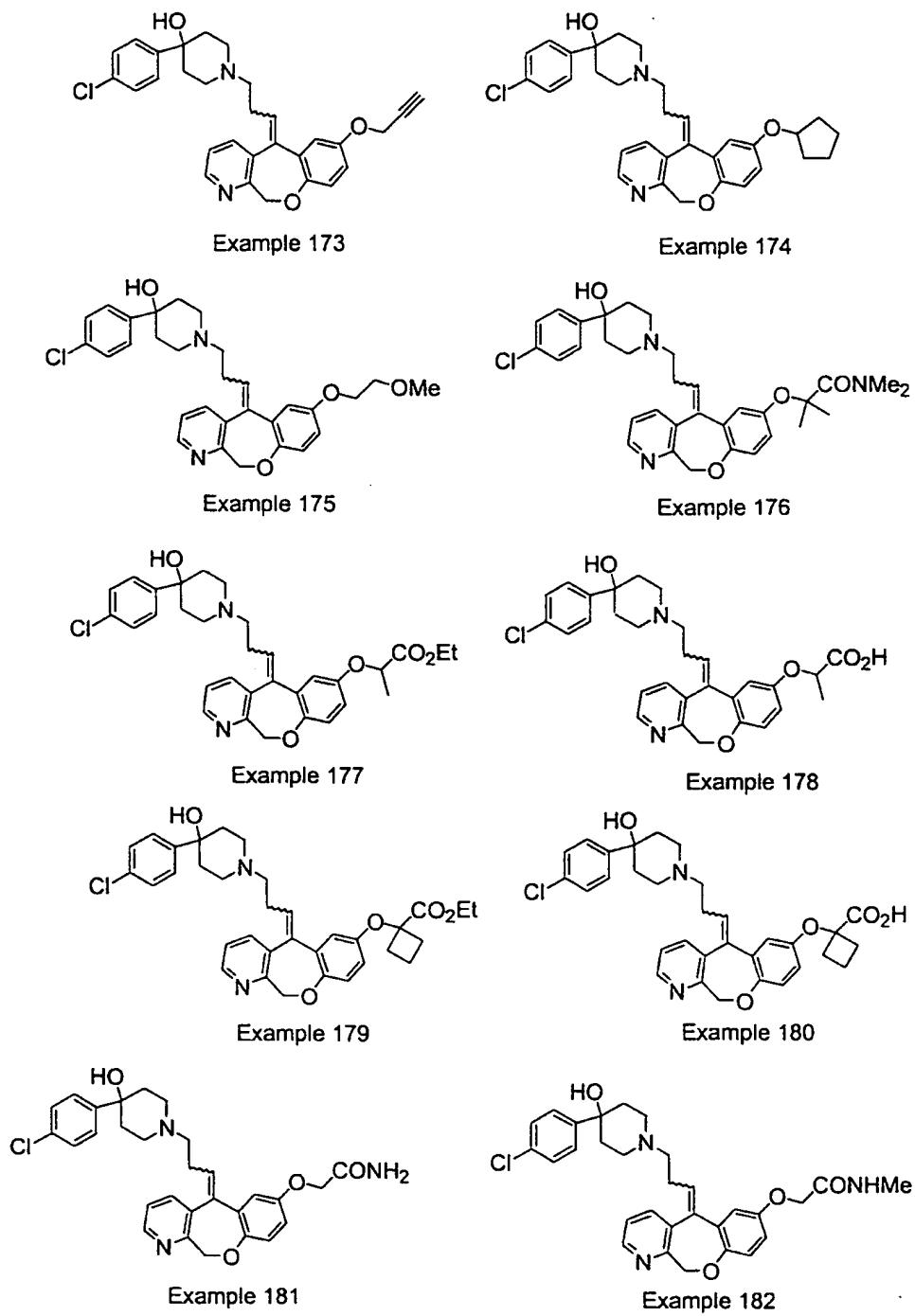
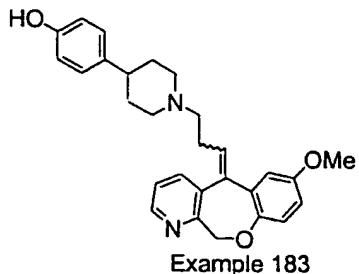
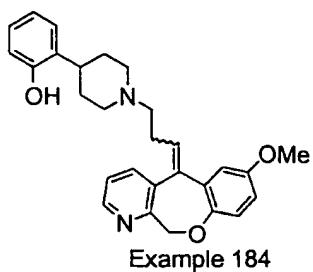


Figure 6R

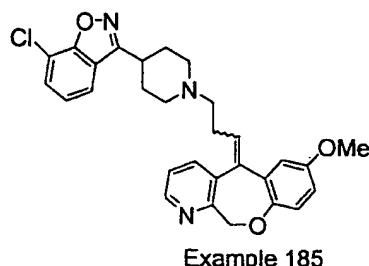
24/32



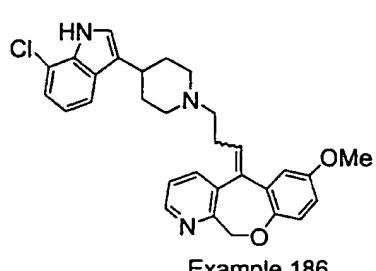
Example 183



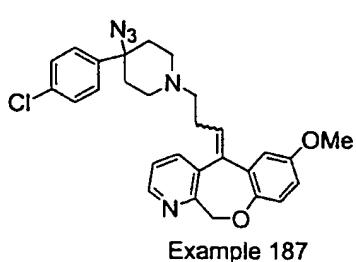
Example 184



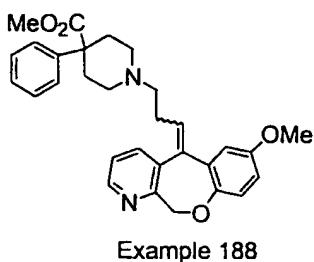
Example 185



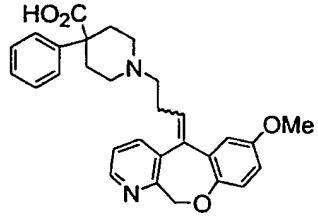
Example 186



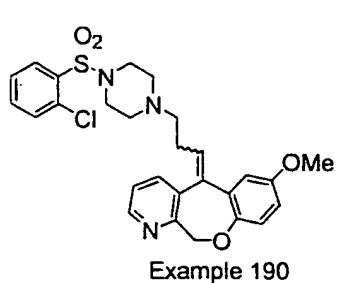
Example 187



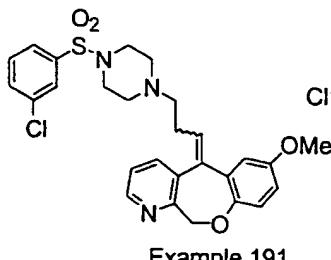
Example 188



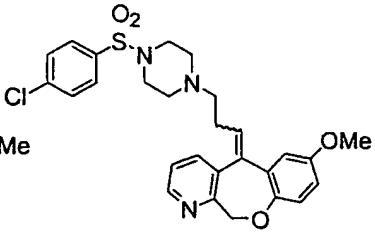
Example 189



Example 190



Example 191



Example 192

Figure 6S

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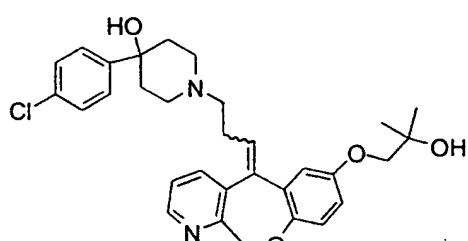
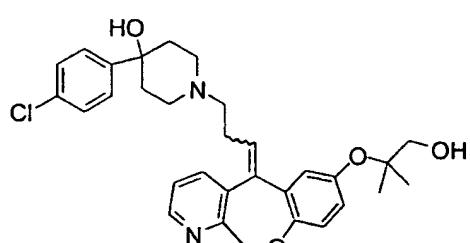
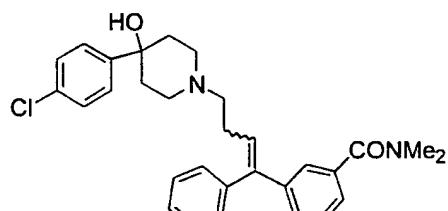
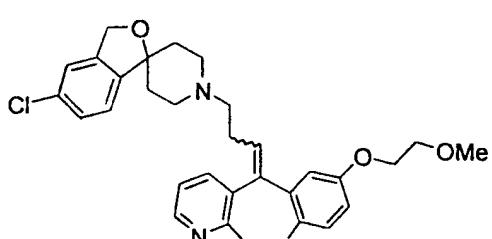
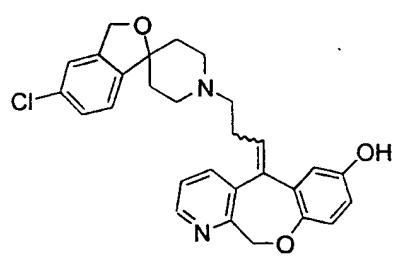
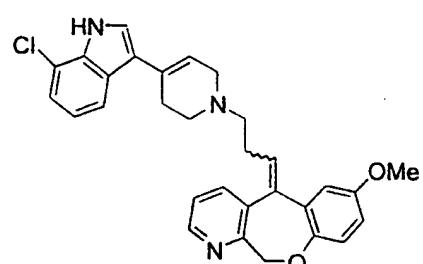
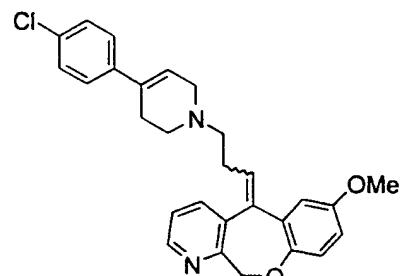
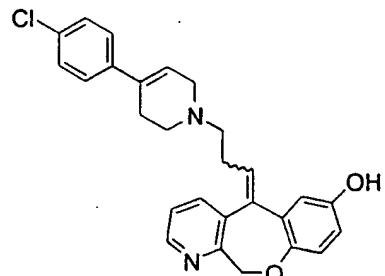


Figure 6T

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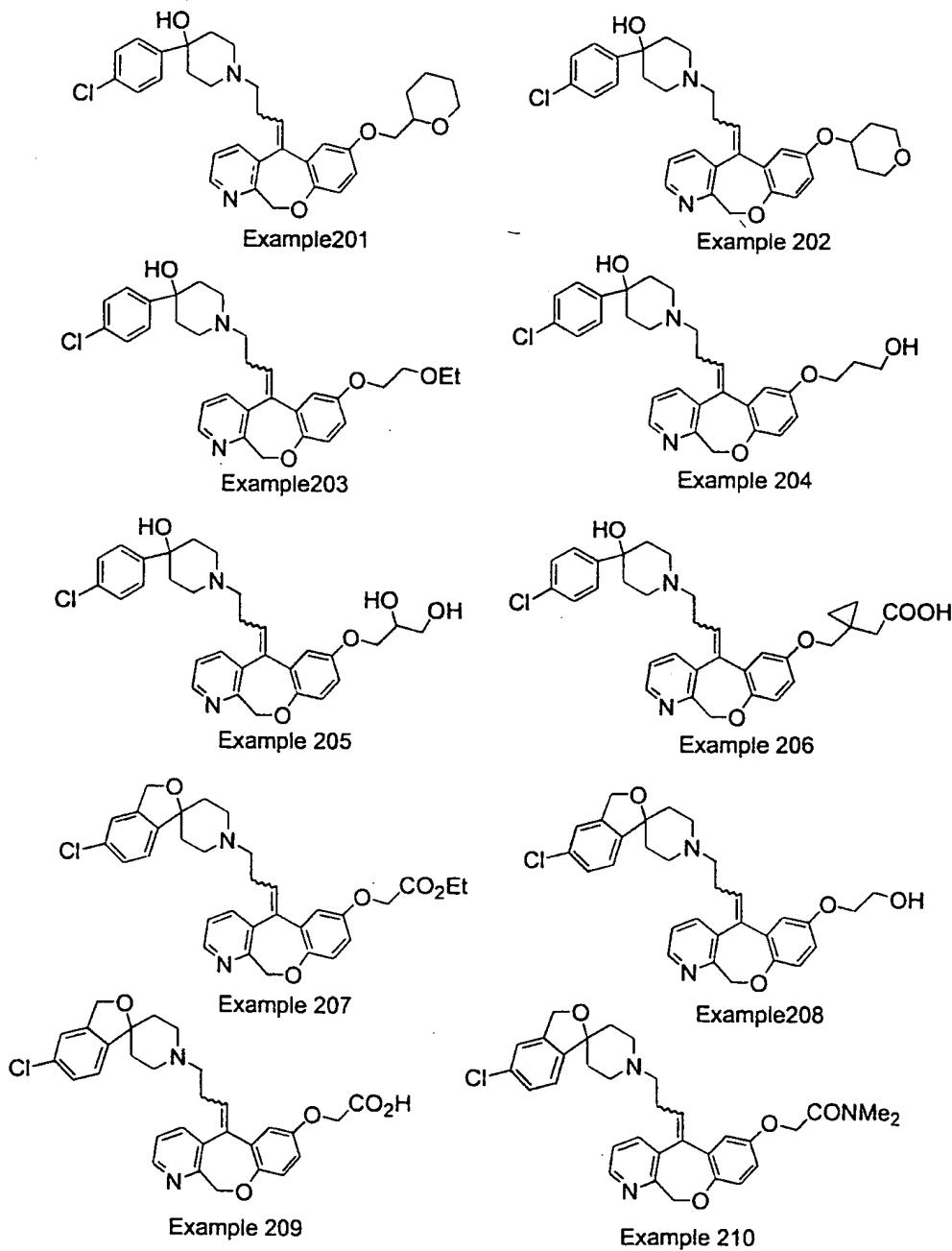


Figure 6U

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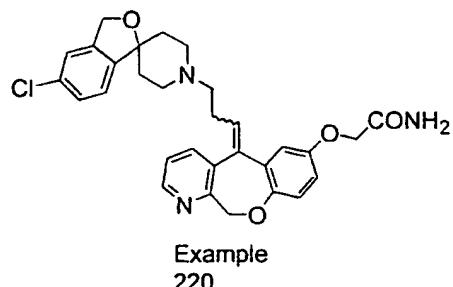
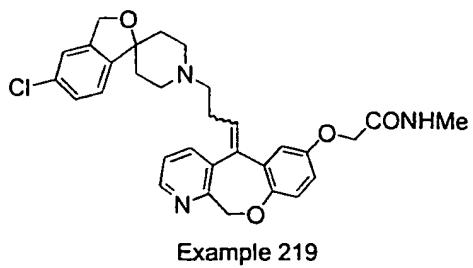
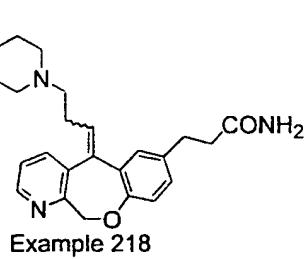
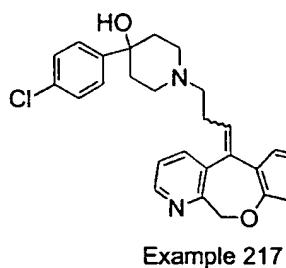
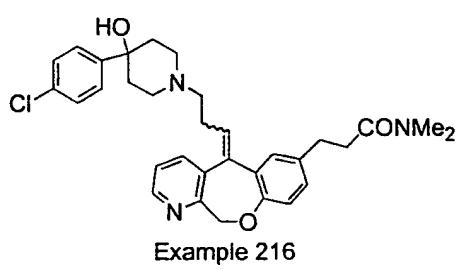
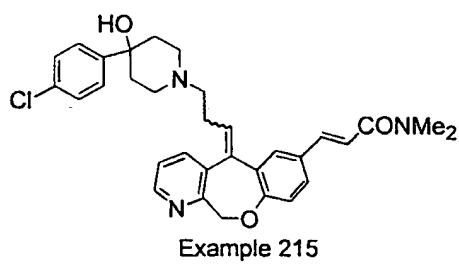
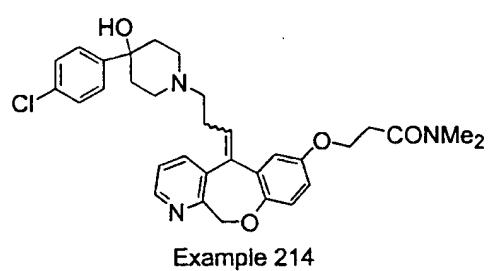
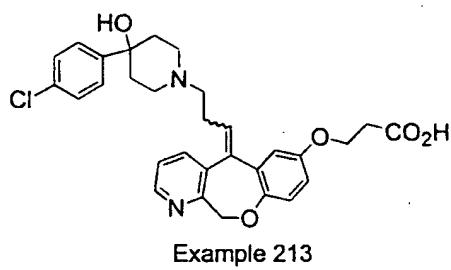
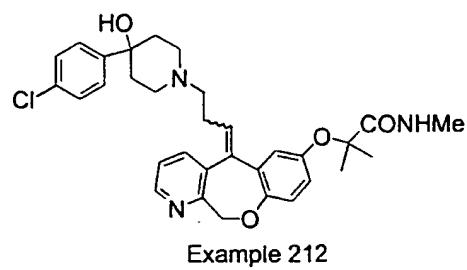
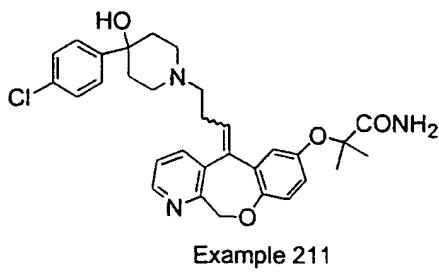


Figure 6V

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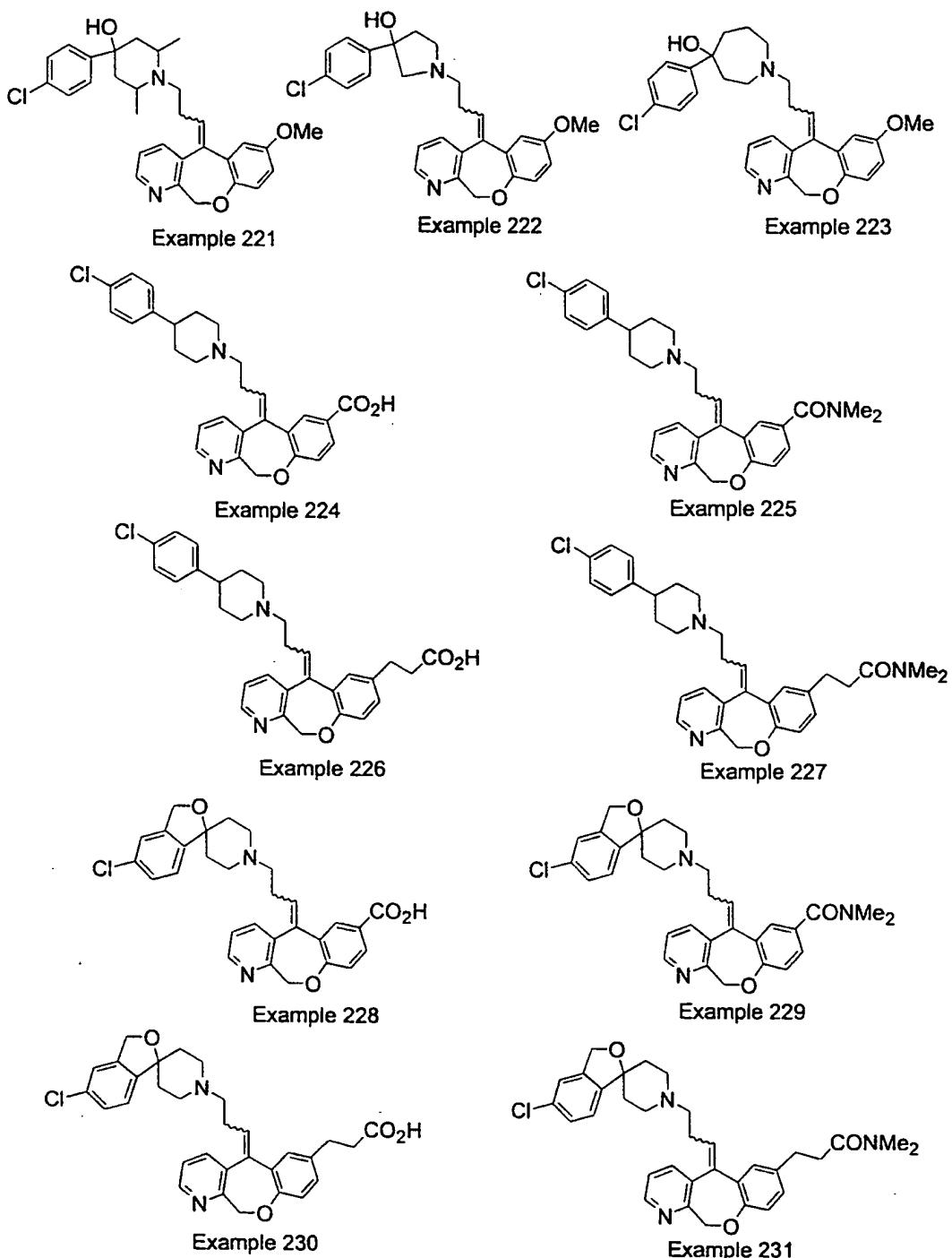
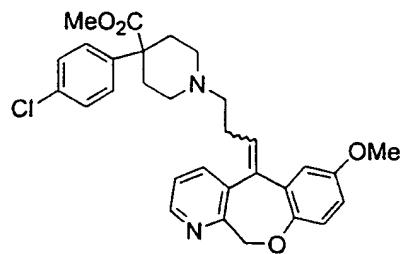
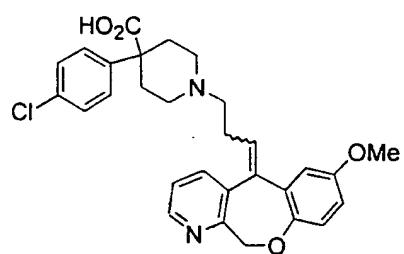


Figure 6W

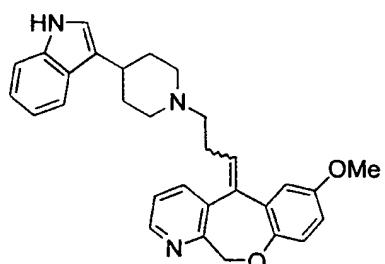
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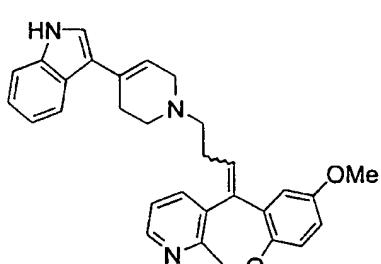
Example 232



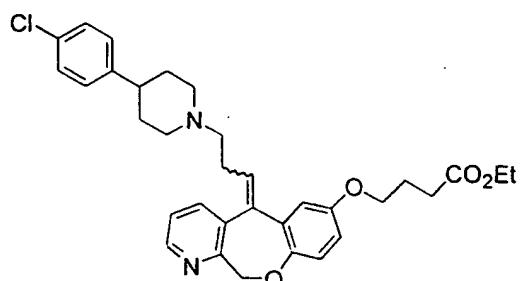
Example 233



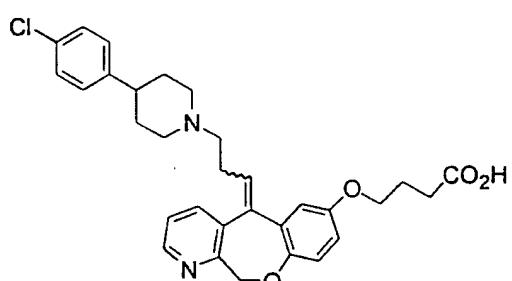
Example 234



Example 235



Example 236



Example 237

Figure 6X

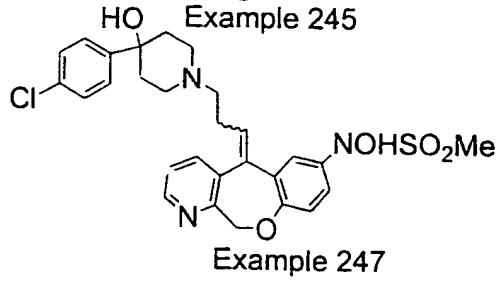
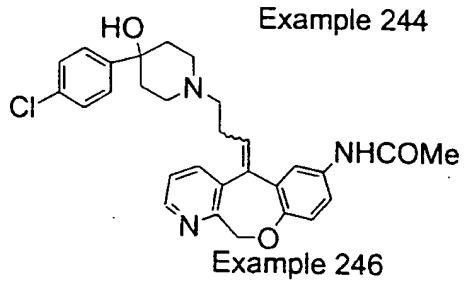
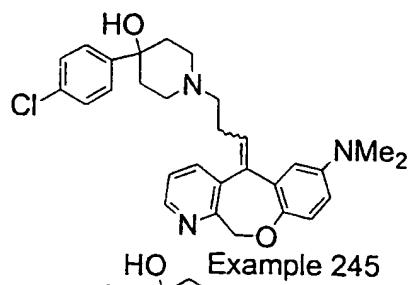
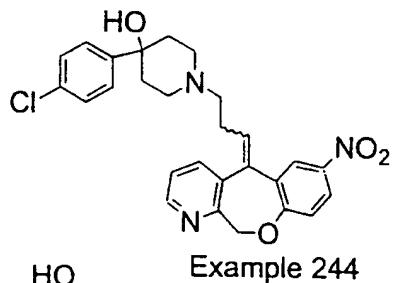
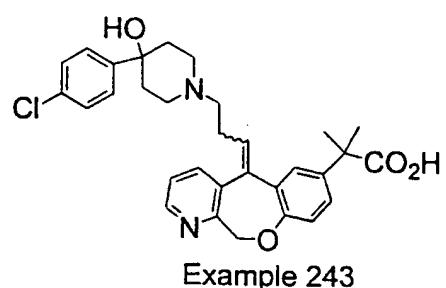
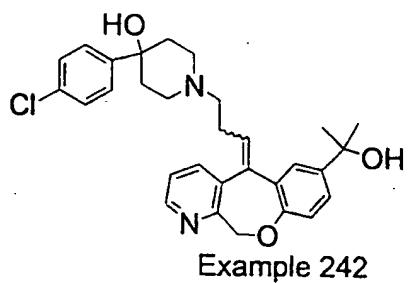
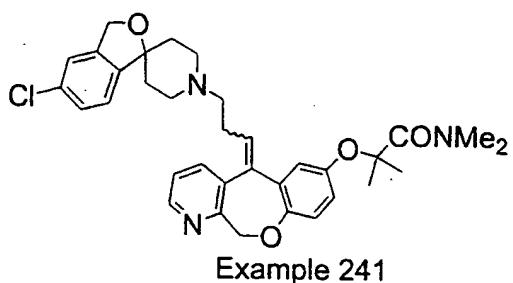
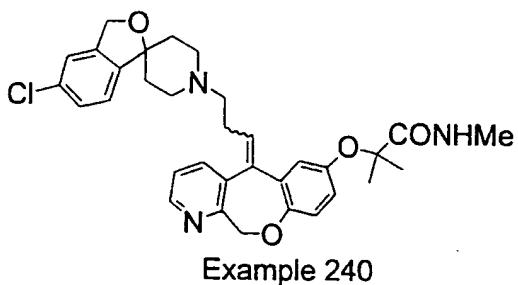
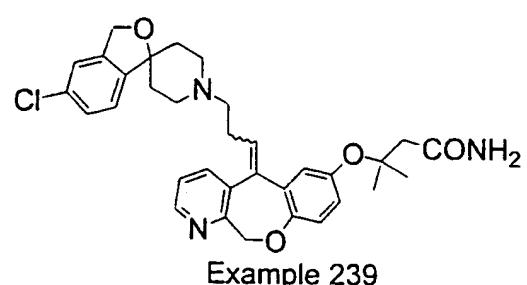
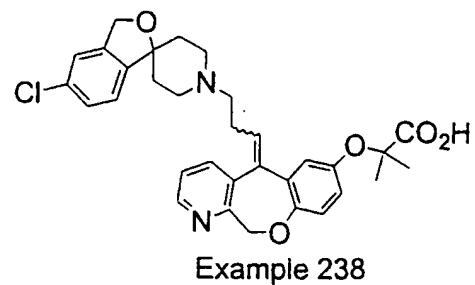
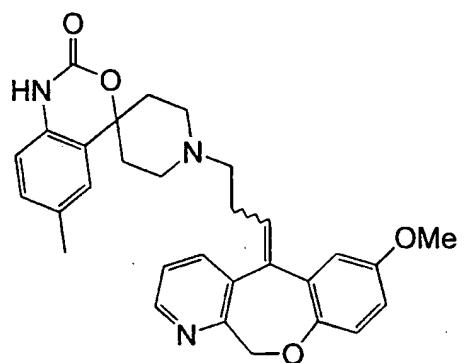


Figure 6Y

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Example 248

Figure 6Z

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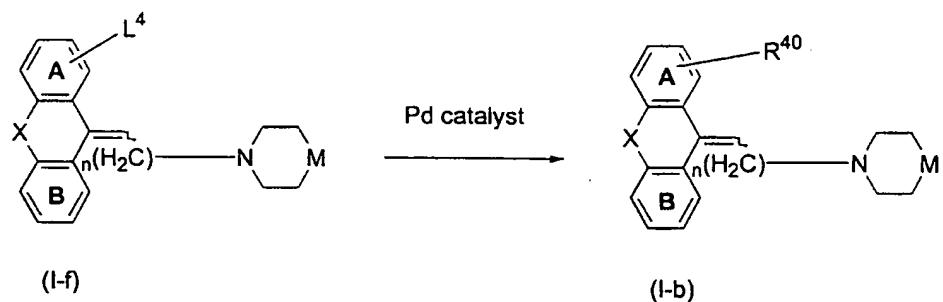


Figure 7

INTERNATIONAL SEARCH REPORT

Int'l. Application No

PCT/US 99/01266

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D491/044	A61K31/445	A61K31/55	A61K31/495	C07D471/04
C07D495/04	C07D519/00	C07D313/12	C07D401/06	C07D409/06
C07D405/06	C07D211/46	//(C07D491/044, 313:00, 221:00),		

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 003 292 A (SANDOZ) 2 September 1965 see example 9 ---	57,76
X	CHEMICAL ABSTRACTS, vol. 93, no. 19, 1980 Columbus, Ohio, US; abstract no. 186323f, EBISAWA: "Benzo'b'1,8!naphthyridine derivatives" page 663; XP002104337 see abstract & JP 08 049377 A (MITSUBISHI) --- -/-	57,76



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 1999	18/06/1999
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

Int'l. Application No

PCT/US 99/01266

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 (C07D471/04, 223:00, 221:00), (C07D495/04, 333:00, 313:00),
 (C07D495/04, 337:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 77, no. 25, 1972 Columbus, Ohio, US; abstract no. 164662h, TSUJIKAWA: "Azathiaxanthene derivatives" page 418; XP002104338 see abstract & JP 07 220200 A (TAKEDA)	57,76
X	DD 80 449 A (KRETZSCHMAR) 12 March 1971 see formula I and table 5 ---	57,76 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

7 June 1999

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl
Fax: (+31-70) 340-3016

Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

Int'l. Appl. No
PCT/US 99/01266

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 81, no. 5, 1974 Columbus, Ohio, US; abstract no. 25566z, K. NAKANISHI ET AL.: "Piperidine derivatives" page 424; XP002104339 see abstract & JP 07 330064 A (YOSHITOMI) 17 September 1973 -----	97
X	GB 1 330 966 A (YOSHITOMI) 19 September 1973 see examples -----	97
X	M. A. DAVIS ET AL.: "New psychotropic agents. VIII. Analogs of amitriptyline containing the normperidine group" JOURNAL OF MEDICINAL CHEMISTRY., vol. 10, 1967, pages 627-635, XP000670146 WASHINGTON US see tables I and III -----	97
X	DE 19 18 739 A (EGYESÜLT GYÓGYSZER-ÉS TÁPSZERGYÁR) 30 October 1969 see example 3 -----	97
X	CH 421 138 A (WANDER) 31 March 1967 see examples 5,6 -----	97
A	WO 97 44329 A (TEIJIN) 27 November 1997 see claims 1,9 -----	1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/01266

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 1 to 56 and 111

are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. Claims Nos.:

because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99 01266

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The search revealed such a large number of particularly relevant documents regarding the novelty of claim 97, that the drafting of a comprehensive International Search Report is not feasible. The cited documents are considered as to form a representative sample of the revealed documents, duly taking into account the compounds illustrated by the examples.

INTERNATIONAL SEARCH REPORT

Information on patent family members				Int'l. Application No PCT/US 99/01266	
Patent document cited in search report	Publication date	Patent family member(s)		Publication date	
GB 1003292 A		NONE			
DD 80449 A		NONE			
GB 1330966 A	19-09-1973	JP 49020790 B		27-05-1974	
		JP 49021150 B		30-05-1974	
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		US 3770729 A		06-11-1973	
DE 1918739 A	30-10-1969	AT 291217 B		15-06-1971	
		AT 298445 B		15-04-1972	
		NL 6905642 A		14-10-1969	
CH 421138 A		NONE			
WO 9744329 A	27-11-1997	JP 9309877 A		02-12-1997	
		AU 3135497 A		09-12-1997	
		EP 0914319 A		12-05-1999	